THE GROWING PROCESS

Introduction

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THIS SYMPOSIUM ON "Advances in Human Nutrition" is fittingly opened with a session devoted to "The Growing Process". We shall discuss human organisms who differ uniquely from the normal adult because they are growing. The pregnant woman, the fetus and the child, the lactating woman—all are growing and creating new substance and, as a result, all have their own, special nutritional requirements.

Dr. Wishik will discuss the nutritional needs of the pregnant and lactating woman. He will emphasize that the fetus is not just a parasite upon its mother. If the maternal diet is inadequate, the fetus cannot grow and develop properly and the possibilities of congenital anomaly, prematurity, stillbirth and sterility are enhanced. He will also emphasize that maternal production of a milk supply, adequate both in amount and in proper components, is intimately dependent upon proper maternal diet.

Dr. György will discuss the unique nutritional needs in infancy, when growth is tremendously rapid and birth weight is doubled in five month's time. He will review for us the advantages of human milk for the infant and will weight the pros and cons of artificial feeding.

Dr. Wilson will discuss nutrition in childhood and the difficulty in deciding upon optimal or even minimal nutritional requirements in the slowly growing, young child under varying conditions of health and disease. He will comment upon nutrition in adolescence, that period of rapid growth when emotional stress, creating problems of food assimilation, of obesity and of reducing diets, may cause malnutrition in spite of attempts to provide an adequate diet.

Dr. Shwachman will survey the difficult problem of proper nutrition for children with various metabolic disorders where, in some instances, specific nutrients must be supplied in abundance and, in other instances, certain nutrients must be minimized or abolished from the diet.

This session, in short, will discuss the nutritional requirements of the growing human organism and their unique variations with age and with disease.

Nutrition in Pregnancy and Lactation

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IN THIS SHORT PRESENTATION, certain items have been selected for discussion because of their temporal and practical interest. Able and exhaustive reviews of the literature have already been made (1–3).

The amazingly delicate balances of the mechanisms of human nutrition are at times subjected to additional stresses over and beyond the ordinary. Growth is one type of stress during which a dynamic balance is maintained despite the net gain in mass. Illness and convalescence constitute other occasions for increased stress.

In illness, as in periods of rapid growth, the occurrence of nutritional disease in the host results from a combination of qualitative and quantitative changes. The qualitative changes are alterations in the nature of one or more parts of the nutritional process, whether ingestion or transportation, intracellular metabolism or other aspects. The quantitative stress is an increased demand for one or many nutrients. A nutritional deficit is more likely to result when the available supply of nutrients is marginal or the intake is marginal, despite ready availability. There are many arguments to support the contention that maternity places as great a variety of nutritional stresses on the host as almost any other life experience.

One of the stresses is an increase in mass—an increase of approximately 20%, chiefly in the last six months of pregnancy (4). This is less than the increase in the first six months of infancy, when a 100% increase usually occurs. During the period of lactation, however, the amount of output of milk in a single month is greater than the increased mass of the whole nine months of pregnancy.

In addition to mere increase in mass, alteration in physiology during the stages of pregnancy, puerperium and lactation is evidenced by the many changes in the activity of the pituitary, the thyroid and the adrenal cortex and the interplay among them, and the changes in the amount or direction of positive or negative balance in items of metabolism as fundamental as those of protein, electrolytes and water. The pregnant woman, for example, stores amounts of nitrogen and structural minerals far in excess of the amounts needed for fetal and maternal tissue stores.

These stresses of increased mass and altered physiology, these quantitative and qualitative changes, take place amidst a strange partnership between the maternal and fetal systems. This partnership is strange because on the one hand there is close communication and an intimate sharing in some respects between the two partners; but in others there is a degree of semi-autonomy, such as different levels of activity of the maternal and fetal endocrine organs and different blood levels of circulating forms of certain nutrients. The dichotomy between the two partners increases as fetal development progresses.

And then to complicate this strange partnership, between the two sits the placenta, not a passive structure but an actively functioning organ, selectively censoring messages in either direction between the partners and from the beginning to the end of the maternity cycle constantly changing the rules under which the partners operate. The placenta prevents the junior partner from taking an undue share. Since the fetus lives off the mother, it is in a sense fully parasitic, but only to the extent that the placenta and the senior partner permit (5).

When a nutrient is available in abundance, the fetus can have its fill. When a supply is marginal, there will be competition between the two, and when the supply is grossly insufficient, the mother is likely to get most. With abundance both mother and fetus are healthy. With gross shortages the fetus may die. When there is marginal supply between

the two extremes—whether the marginality is due to geography, economics, culture or individual choice—this is the situation of greatest interest to the medical and nutrition professions.

The outcome of competition between mother and fetus varies with each nutrient. Among those which the mother greedily takes for herself are vitamins A (6) and E (7) both showing much lower levels in the fetal than in the maternal blood. Iodine shortage may produce congenital cretinism (8), or riboflavin deficit may produce a severe congenital malformation (9) without appreciable disease in the mother. Admittedly oversimplifying an extremely complex matter, we might say that the mother tends to hog certain nutrients.

On the other hand, fetal stores of iron and vitamin C (10, 11, 12) to levels twice those of the mother and higher occur while the mother's levels of these nutrients drop far below the nongravid amounts. We cannot, however, merely compare the occurrences during pregnancy with those of nonpregnancy as the norm. The pregnant woman seems to establish new types and levels of adjustment. For example, vitamin B_{12} in the maternal tissues drops in storage levels as demonstrated by animal experiments and studies of the liver and kidney. The fetal blood level of B_{12} is invariably higher than the mother's. The mother has an increased capacity to absorb and take up B_{12} and yet her tissue stores are lower (13). Her increased capacity has been attained chiefly for the benefit of the fetus. This is an alteration in physiology from the nonpregnant norm. The nutritional stresses of pregnancy are not lightened by factors that affect the woman's intake of food, such as nausea and vomiting, psychologic reactions to eating and to foods, and sometimes confusing professional advice.

What are some of the possible undesirable results of nutritional disturbance in maternity? There are undesirable outcomes for the mother and for the fetus. For the mother, we of course are concerned about survival, her retaining good general health and the possibility of her developing a poor nutritional state during pregnancy and especially as a residual after it. In this country, as in all parts of the world, a very common diagnosis among pregnant women is anemia. The hemoglobin level of the mother's blood drops. There are also, however, a rise in blood volume by dilution with actually a 15% rise in total circulating hemoglobin and a shift to the right of the oxyhemoglobin dissociation curve, with a consequent greater oxygen-carrying capacity of the pregnant woman's blood (14). Like B_{12}, the lower hemoglobin level which we call anemia has been acquired in the building up of the fetal stores and it may possibly be physiologically adequate for the mother during pregnancy.

The fact that iron treatment does raise the level of hemoglobin is worth noting but it does not prove that that higher level is necessary or desirable during pregnancy. Until further study, however, we must continue to advise iron treatment. It is well-known, at least, that subsequent anemia in the child is related to maternal anemia.

Other threats to the mothers from nutritional deviations, with varying degrees of experimental and clinical substantiation, are obesity, aggravation of pregravid health conditions such as tuberculosis, pregnancy complications such as toxemia, interruption of pregnancy early or late in pregnancy and poor lactation capacity post partum.

What are the hazards to the child? Is there a possible influence on his birth weight, so that he may be born too small or too large? Evidence suggests that the degree of adequacy of the diet does affect the size of the baby somewhat (5). On a superior diet babies are larger, but the mothers have a more normal course during labor and delivery, not greater difficulty from that larger baby. And there is no increase in birth injury in this group (15).

Also, a low protein intake in the latter part of pregnancy will produce a lighter, shorter baby, but in poorer general health with less chance of survival (5). This means that we should once and for all discard completely the notion that dietary restriction should be practiced so as to have a smaller baby and an easier delivery.

A second threat to the fetus is that of congenital malformation. Animal experimentation has given convincing evidence of production of different types of congenital malformation by deprivation during pregnancy in a large array of nutrients (16); to mention a few, vitamins A, B_{12}, C, niacin, riboflavin, pantothenic and folic acids, iodine, oxygen, and calcium and other minerals. As yet, how-

ever, we do not have adequate substantiation in humans, for obvious reasons (17). The ethics of research will tolerate voluntary temporary and reversible food deprivation in an adult but we cannot take chances with possible effects upon an unborn child.

Also, our techniques of measurement are still crude. A one-day deficiency in certain amino acids can produce detectable change in enzyme function in animals or even throw a person into negative nitrogen balance. We have still to develop methods for studying subtle transient factors.

What kind of diet, then, should be recommended? The Food and Nutrition Board of the National Research Council has issued the Recommended Allowances of Nutrients During Pregnancy (18). While these do not follow the belief that the pregnant woman has 'to eat for two,' they do give consideration to the greater needs that exist then than during the nongravid state. They call for a 15% increase in calories, 35% in protein and appreciable rises in calcium, iron and the more commonly known vitamins. The amounts that are recommended are intended for the last five months of pregnancy and not the first four.

To quote from Thomson and Billewicz (19): "The recommended allowances for pregnancy depend more upon observation of the diets ordinarily taken by healthy pregnant women with a good reproductive performance than upon intimate knowledge of the physiological effects of the nutrients involved. These allowances are, therefore, empirical and practical rather than physiological standards." For this very reason, the Research Council carefully used the word 'allowances' rather than 'requirements.' Nevertheless, the allowances are intended to be levels of intake as goals for most pregnant women. This is important to emphasize in relation to the matter of dietary restriction, which will be discussed later in this paper.

Probably the specific nutrient which American physicians most commonly restrict in the diet of pregnant women is salt. This practice is based on a considerable body of evidence. Positive sodium balance exists through most of the course of normal pregnancy, with a consequent increase of about 10% in the total exchangeable sodium (20). Water retention also occurs as a constant feature of pregnancy. Water retention may be due to low plasma protein level, the enormous steroid sex hormone activity, or to high sodium intake (21). In pre-eclamptic patients, the total exchangeable sodium increase is greater than usual; and women with abnormally high extracellular water level, as measured by some workers by the thiocyanate test, have been found to have six times the pre-eclampsia rate of women with lower levels (20).

Arguments on the other side can also be advanced. Although low salt diet reduces the available water level volume, it does not necessarily prevent toxemia (21). In a recent British medical journal there appeared an interesting and provocative article by Dr. Robinson (22) in which she reported that she could prevent eclampsia by increasing salt intake during pregnancy. In the treatment of hypertensive toxemia of pregnancy, a low salt diet of 30 mEq of sodium or less per day is usually prescribed and often obtains a favorable drop in blood pressure and serum protein level and a decrease in edema and proteinuria. Failure to obtain such a favorable response usually has been considered indication for termination of pregnancy. Recent reports have described a response in some instances to the opposite—intravenous treatment with sodium chloride—in the belief that this so-called 'low salt syndrome' resulted from low salt intake in the presence of low adrenal cortical function or altered placental steroid metabolism (23).

The nonpregnant adult can remain in sodium balance on as little as 10 mEq of sodium per day. Most people take more than ten times that amount. In the other direction, the body can handle 600 mEq a day, a capacity range of 6,000 %. It may be that salt restriction is not necessary for most pregnant women. Again, we need more evidence before we can draw definite conclusions.

Other than salt, the most common dietary restriction prescribed by American physicians is the limit on total caloric intake, as determined indirectly through the mother's weight gain during pregnancy. What basis exists for this practice? Undoubtedly excessive weight gain increases fatigue and discomfort in the latter months of pregnancy and contributes to varicosities. There is no evidence, however, that heavier women have more difficult labor

or delivery. The woman or her husband may be concerned that she will not regain her prepregnancy figure. A study of a large number of women shows that the average amount of weight retained even for six weeks postpartum was about 4 pounds (4). It is remarkable how quickly most women revert to their prepregnancy weight and, fortunately, to their prepregnancy wardrobe.

The chief reason for restricting caloric intake and weight gain during pregnancy, however, is not these other considerations but the fear of toxemia. Toxemia is associated with fluid retention; therefore, with weight gain. It does not follow that weight gain produces toxemia. On the contrary, evidence suggests that insufficient weight gain in the first and second trimesters of pregnancy is more often associated with subsequent toxemia and prematurity (24, 25). "It is frequently recommended that the obese patient's gain in weight during pregnancy should be markedly restricted and by some it is suggested that they be made to lose weight. It is of clinical importance to note that when the pattern of gain in these obese women was 8 pounds or more below the average, the incidence of actual pre-eclampsia was approximately doubled" (25).

There is a natural tendency to believe that a woman who was far above average weight before pregnancy should be allowed to gain less weight during pregnancy. Warkany makes this statement: "The stores of maternal tissues act as buffers which prevent deprivation of the developing embryo as long as possible" (9). It seems unwise, therefore, to divert these stores of the obese woman from the fetus to feed the mother as well as the fetus. There is strong indication that it is unsafe to try to correct overweight during pregnancy (5). It is better to wait until afterwards.

The bulk of nutrition studies that may be found in the literature highlight deficits in diet during pregnancy. There is no definite evidence that gain in weight without edema is harmful. Yet, so much of diet advice given in this country to pregnant women focuses on restricting diet rather than increasing essential nutrients. It is very difficult for a woman to do both. It is not easy to consume 80 gm of protein per day on any diet, let alone a low caloric one. There is no justification for placing all pregnant women on some kind of routine low caloric diet, whether 2,000, 1,500 or even 1,200 cal. as is being done so commonly. This is at variance with the recommendations of the National Research Council. And to restrict intake during pregnancy merely because a woman was overweight before pregnancy has strong arguments against it.

When we add up the total number of pounds of the baby, the placenta, the amniotic fluid, retained water, increased size of uterus and breasts, it is difficult to keep the total much below 30 pounds (14, 26). A review of many studies shows that women who experience normal pregnancy and have normal babies gain an average of 24–27 pounds (26, 27), and one out of six of these (and remember these are normal pregnancies) gains more than 35 pounds (26). Yet the average, whether 25 or thereabouts, is often established by physicians as an arbitrary ceiling for all. The average is made the permitted maximum in practice.

Women in our society have numerous fears and guilt feelings with respect to pregnancy. We should not increase these with constant worry about an impossibly restricted dietary regimen with ever-present fear of the doctor's criticism. Instead, we can help women so that pregnancy will be the happy time that it should be.

The special nutritional demands of lactation are even greater than during pregnancy. There should be an increase of about 30% in fat over the nonpregnant diet (2). Vitamin C even on high intakes drops appreciably in the mother's serum (28). Calcium, proteins, calories and vitamins are also needed in increased amounts (18).

The most significant body of findings of various studies tells us that undernutrition prior to pregnancy and extending into the first months of pregnancy is a strong factor in all types of unfavorable outcomes—undernutrition prior to pregnancy (29, 30). This adds another argument to the many others for focusing our education and health supervision on the preconceptional and interconceptional periods rather than on the prenatal period alone.

The challenge to nutrition workers is well stated by a group of research workers in Aberdeen, Scotland (31): "The nutritional

status of a pregnant woman depends more upon her life experience of diet than upon the nature of the diet she happens to take during pregnancy."

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Nutrition In Infancy

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PROGRESS IN INFANT NUTRITION, especially in its broad aspects, is a shining example of a purely clinical and empirical approach. Apart from the accessories, by no means unimportant, of the infant dietary such as vitamins and minerals, the basic rules in the nutrition of the infant which should determine the requirement for calories, protein, carbohydrates and fat were formulated through observations in the clinic and not through animal experimentation.

Animals differ in their growth rate and, in consequence, necessarily also in their requirements for calories and body-building food constituents, in the first place protein, from human infants. Furthermore, there is no animal known or available for experimentation with the long sucking period of the human infant. Thus, it is understandable that human milk, certainly the physiological complete food for the human infant, received no particular attention by experimental nutritionists working with animals. From a purely teleologic point of view, human milk must be considered superior to cow's milk as the initial food for the human infant. In teleologic language: human milk is for the human infant and cow's milk is for the cow.

For the human infant, cow's milk remains a substitute food. However, human milk is not always available nor is breast feeding always possible. Certain cultural anthropological factors plus lack of proper educational preparation of the mother makes breast feeding, even when possible, a difficult goal to achieve. It is certainly discouraging that society subordinates breast feeding to a secondary position in infant feeding. There is ample evidence to support the theory that with good aseptic care it is difficult to do harm, or at least to cause demonstrable harm to a normal infant kept on any feeding regimen, providing the regimen covers the minimum requirements for all essential nutrients. When using cow's milk or other formulae, the greatest benefit in successful infant feeding has been reached by following proper aseptic rules: pasteurization, autoclaving and other related procedures.

The trend in modern pediatric practice turns to maximal growth.

Even half-diluted cow's milk contains more protein and salt than human milk. It is claimed that the increased supply of protein and salts leads to increased rate of growth through retention of nitrogen and salts. Should it be, therefore, concluded from such observations that cow's milk is superior to human milk? Or conversely, that better weight gain and steeper weight curves are to be preferred under all circumstances to the average obtained with human milk? Can physicians be sure that accelerated weight gain and overfeeding in infants are only temporary interludes and will have no lasting effect which might manifest itself perhaps years or even decades later in adult life? Be that as it may, there is no reason to believe that maximal weight gain and accelerated maturation in infancy should be the optimal human nutritional goal. From a purely practical point of view, infant nutrition as it is used today under strict rules of hygiene yields good results: cow's milk formulae, mixed feeding, even when, as is now customary, at an early age, vitamin supplements will support satisfactory growth and development in a normal infant.

A quotation from a recent report of the Committee on Nutrition of the Academy of Pediatrics summarizes the present status very well, and I am quoting: "The practice produces neither beneficial nor harmful results but rather attests the adaptability of the baby to the whim of his caretakers" (1).

It is another question whether modern infant nutrition may be considered truly optimal without causing unnecessary, even if

through compensation only transient, stress or perhaps even damage which might manifest itself in later age.

It is extremely difficult, well nigh impossible, to define 'optimal' nutritional state. Increased 'natural resistance' is certainly one outstanding attribute of excellent health. Those of us, like myself, whose pediatric experience dates back many decades, will have no hesitation to testify in favor of human milk as the best therapeutic diet for infants with severe chronic pyogenic infections. In general, this effect of human milk in a variety of infections was ascribed not so much to the presence of specific antibodies but to the action of unspecific factors of unknown origin. Transfer of immune bodies from ingested human milk through the intestine into the blood is a negligible factor in resistance to disease if it occurs at all. Improved general hygiene and the use of antimicrobial agents have of late obscured the superiority of human milk over cow's milk in regard to the figures of morbidity and mortality. Recent statistical studies, however, published from by no means underdeveloped countries like the United Kingdom and Sweden, indicate that these differences may be demonstrable not only under very poor but under good hygienic conditions.

Table 1 summarizes (2) a rather impressive number of observations regarding morbidity and mortality in infants exclusively or partially breast-fed or bottle-fed from Manchester (England). The significantly lower figures for mortality and morbidity in breast-fed, even in partially breast-fed, infants is of interest. This conclusion applies not only to gastrointestinal but also to respiratory infections, including otitis. In table 2 the much larger number of days with elevated temperature in bottle-fed infants of all age classes, especially around 4–8 months of life when compared with breast-fed infants is certainly impressive. This study was carried out in Sweden (3). In a more recent and still unpublished study of Dr. Vahlquist also in Sweden, the same observations have been confirmed.

A second distinctive feature regarding infants fed human milk as compared to those fed cow's milk refers to the intestinal flora and the reaction of the feces. In contrast to the acid reaction of the feces of normal breast-fed infants, the pH of the feces in infants given the usual cow's milk formulae falls in the neutral or alkaline range. Unlike the mixed intestinal flora of infants on cow's milk formulae, the intestinal flora of healthy breast-fed infants is characterized by the prevalence of a particular species of *Lactobacillus*, namely, *Lactobacillus bifidus*.

In the course of investigations on the metabolic requirement of various strains of *L. bifidus* isolated from the feces of young infants, we encountered in our laboratory an apparently specific variant of *L. bifidus* which

TABLE 1. RELATION BETWEEN FEEDING AND MORTALITY AND MORBIDITY

Feeding	No. of Infants	Mortality	Morbidity	Case-Mortality
		per 1000	*per 1000*	%
Breast-fed	971	10.2	223.4	4.6
Partly bottle-fed	1441	25.7	464.2	5.5
Bottle-fed	854	57.3	573.7	10.0
Total	3266	29.3	421.3	6.9

TABLE 2. INFECTION AND NUTRITION

Age Groups, Months (three-month periods)	0–2	1–3	2–4	3–5	4–6	5–7	6–8	7–9
Breast milk								
Total days of observation	1,377	1,709	1,578	1,248	923	665	430	235
Days with fever 38.1° and above	3	5	6	8	7	6	2	4
Days with subfebr. temp. 37.6°–38.0°	26	45	59	86	85	66	23	4
Total days with rise in temp. 37.6° and above	29	50	65	94	92	72	25	8
Artificial food								
Total days of observation	1,151	1,664	1,853	1,771	1,547	1,219	952	630
Days with fever 38.1° and above	1	10	12	20	29	34	37	24
Days with subfebr. temp 37.6°–38.0°	52	99	146	158	165	129	94	45
Total days with rise in temp. 37.6° and above	53	109	158	178	194	163	131	69

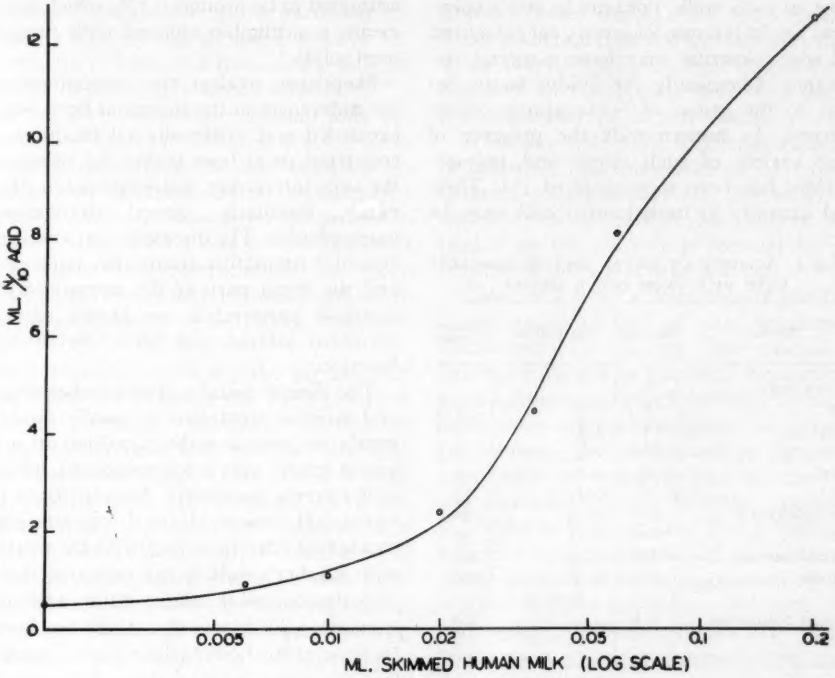


FIG. 1. Microbiological growth effect of human milk.

TABLE 3. ASSAY OF HUMAN AND COW'S MILK

Supplement		Titration
per 10 ml. of medium	*ml*	*ml. N/10 NAOH*
None		0.4
Human milk (skimmed)	0.02	2.2
	0.06	7.9
	0.2	12.5
Cow's milk (skimmed)	0.1	0.6
	0.3	0.8
	1.0	2.3

was named *L. bifidus* var. pennsylvanicus (4). On primary isolation only scant growth was observed. Further propagation in consecutive subcultures was achieved when human milk was added to the medium (5). With increased supplements of human milk to the original liquid medium, acid production as an index of bacterial growth increased exponentially towards a maximum (fig. 1), indicating that a constituent of human milk must be an essential growth factor for *L. bifidus* var. pennsylvanicus (5). With average samples of human milk half-maximal growth was reached with about 0.06 ml of whole or skimmed milk added to 10 ml of the basal liquid medium. In contrast, cow's milk was practically inactive. In the first example shown in table 3, the ratio of activity of cow's milk to human milk was about 1:50. A similar ratio of activity, with an average of 1:40, was found with other samples of human milk and cow's milk. Thus with regard to this microbiological growth factor, the activity of cow's milk is definitely of a lower order of magnitude than that of human milk.

The 'bifidus factor' in human milk is not destroyed or altered in its activity by autoclaving. Human milk ash was inactive.

In further studies the activity of human milk was compared with that of the milk of other species (table 4). The average relative activity was the highest for human colostrum, closely followed by rat colostrum, than by human milk, rat milk, cow's and sow's colostrum. All the other milks tested, in particular the milk of ruminants, such as cows, sheep and goats, have shown only very slight activity (6). The high titre of the bifidus

factor in early milk, not only in cow's colostrum, but in human colostrum, rat colostrum and sow colostrum may have a special significance. Chemically the bifidus factor belongs to the group of N-containing carbohydrates. In human milk the presence of great variety of such oligo- and polysaccharides has been demonstrated (7). Their total quantity in fresh human milk may be estimated to be around 0.7 %, which is by no means a negligible amount with respect to total solids.

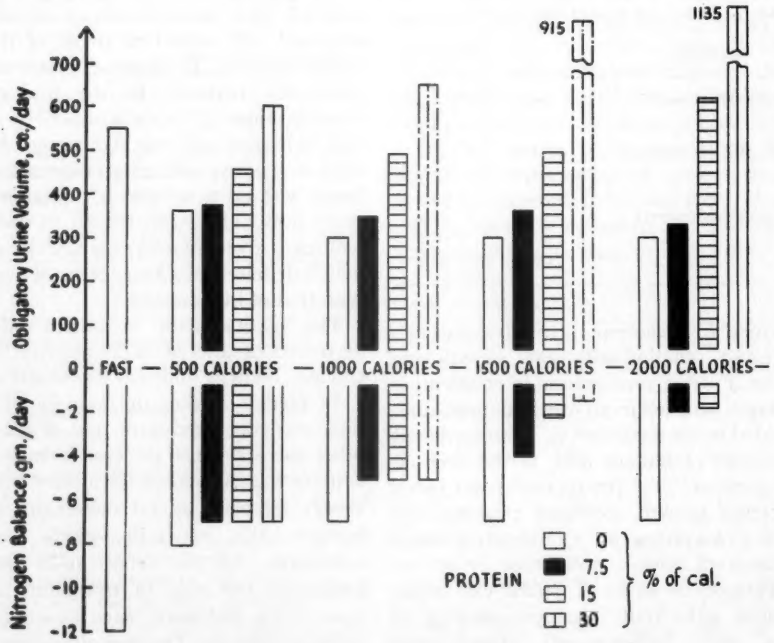
Table 4. Activity of human milk as compared with milk from other species

Species	Activity	One Unit in	Relative Activity
		ml	
Guinea pig	0		
Cow	(+)	2.5	2.5
Sheep	(+)	2.5	2.5
Goat	(+)	2.5	2.5
Mare	+	0.5	12
Sow	+	0.4	15
Cow colostrum	++	0.15	40
Rat	++	0.13	45
Rat colostrum	++	0.03	200
Human	++	0.06 (0.02 to 0.15)	100
Human colostrum	++	0.02 (0.01 to 0.03)	300

Skepticism against the overestimation of the differences in the intestinal flora between breast-fed and artificially-fed infants is best countered or at least shaken by reference to the very interesting, not well-known disease-entity, familiarly named Acrodermatitis enterophatica. The disease is characterized by vesicular dermatitis around the body orifices and the distal parts of the extremities, with multiple paronychia on hands and feet, diarrheal attacks and other digestive dysfunction.

The disease usually appears after weaning and without treatment is usually fatal. Recently we observed the condition in a very young infant, only a few weeks old, fed cow's milk formula since birth. Brandt (8), in 1936, stated that "among all the therapeutic experiments that have been instituted the treatment with mother's milk is the only one that has any demonstrable effect. After addition of mother's milk to the diet, there has been an increase of the body weight from a previously

Table 5. Effect of protein intake on obligatory urine volume and nitrogen balance



almost arrest of growth, and in particular the general condition has shown a distinct improvement. . . Diets free from cow's milk or addition of goat's milk were ineffective."

In our own observation, human milk has also shown beneficial effect but unfortunately the supply was exhausted before complete remission was obtained. More recently the intestinal antiseptic Diodoquin has proved to be a very effective remedy in the treatment of Acrodermatitis enteropathica (9). The nature of this intriguing condition is unknown, it is probably based on an inborn metabolic error.

The newborn, especially the prematurely born infant, is at birth not fully endowed with all metabolic enzymatic equipment which characterizes later age periods. The renal function reaches its maturity at the age of 4, perhaps even only 6 months. In its immature state, especially in the newborn period, it shows impairment of concentrating power. In consequence it handles with difficulty abnormal loads as represented by electrolytes and metabolic products of protein.

Cow's milk, with its high content of salt and protein, will be handled with difficulty in concentrated form, as will any other form of food with higher protein content than the more dilute foods.

Table 5 summarizes observations on adults (10). With 2000 cal. and no protein in the diet, the nitrogen balance is extremely negative. The loss of water, expressed by the obligatory urine volume, is about 300 cc.

With 7.5% of calories in form of protein, which interestingly enough is just the same as present in human milk, and with still 2000 total cal. we can improve considerably on the nitrogen losses and, in the same time, the urinary volume does not increase very much. These observations were done during the last war and the conclusions have been used for the preparation of life raft rations.

If we use 15% of the total calories in form of protein, the improvement in nitrogen balance is negligible but the water loss doubles; this means that the life span of the person on the life raft is reduced by 50% because of thirst and dehydration.

Table 6 is from a statement of the Committee on Nutrition of the Academy of Pediatrics (11). In the last column the figures for 'Water in Excess of Expenditures' show a satisfactory positive balance for human milk even at high environmental temperature. In contrast, the corresponding figures for cow's milk are negative and for the usual cow's milk-water-sugar formulae uncomfortably close to the zero-line. This is the reason why with high environmental temperature or in the presence of fever, supplement of water is recommended for infants fed such cow's milk formulae. However, the fact remains that it must represent a stress for the infant. Even with added water, the metabolic stress is demonstrable by the changed homeostasis, i.e. high figures for BUN, inorganic P and reduced Ca in the serum of young infants fed concentrated cow's milk formulae. In the light of these similar observations it is not surprising to find in the most recent revision (1958) of *Recommended Daily Dietary Allowances*, published by the Food and Nutrition Board of the National Research Council–National Academy of Science, no recommendation for infants for the first month of life and no figures for protein-allowances during the whole first year of life. The fol-

TABLE 6. OSMOLAR LOAD AND WATER BALANCE

	Supply of Water			Expenditures of Water					Water in Excess of Expenditures	
	Preformed water*	Water of oxidation	Total water	Renal	Extrarenal at 21°C	Extrarenal at 34°C	Total at 21°C	Total at 34°C	At 21°C	At 34°C
Human milk	200	13	213	20	80	147	100	167	113	46
Cow's milk	200	13	213	87	80	147	167	234	46	−21
Cow's milk plus carbohydrate†	200	13	213	61	80	147	141	208	72	5

* For concentration of 150 ml/100 cal (20 cal/oz.)

† Two-thirds of the calories from cow's milk and one-third from added carbohydrate.

lowing statement is especially revealing: "Breast feeding is particularly indicated during the first month when infants show handicaps in homeostasis due to different rates of maturation of digestive, excretory and endocrine function."

To discuss further the immaturity of the newborn infant, more and more data are accumulating to testify to the immaturity of the young infant, especially of the premature infants. About twenty years ago, Levine, Marples and Gordon found in premature infants fed their recommended high protein formula that they excreted in the urine large amounts of a parahydroxyphenyllactic and parahydroxyphenyl pyruvic acid. They also reported that with the addition of ascorbic acid this excretion has been reduced practically to zero. They related this finding to a disturbance or immaturity of the tyrosine-oxidase system (12, 13).

Kretchmer and his associates (14, 15) showed that the catabolism of phenylalanine may also be impaired at birth. In particular, they found that the activity of phenylalanine hydroxylase is negligible in the livers of rats late in gestation and in the early neonatal period (16). This immaturity of the tyrosine-system is reminiscent of the injury of the same system observed as sequence of tourniquet shock (17, 18), and may have a similar or closely related foundation.

Even more interesting are studies on the immaturity of red blood cells in newborn infants and especially in prematures. Recently Gross and Hurwitz (19) have found high values for glucose-6-phosphate dehydrogenase, aldolase and 6-phosphogluconic dehydrogenase. The increased metabolic activity of red blood cells in the newborn, and for a larger period of time in prematures may be linked to glycolysis and to the 'pentose-shunt,' with gradual decline to values found for adult subjects, in the second 6 months of life. The reduced glutathione is not lowered in amount but it is unstable in the red blood cells of newborn infants. This instability of reduced glutathione is found as genetic attribute in persons with hemolytic tendency after administration of plasmaquine, naphthalline, furadantoin and related substances (20–22).

Of interest is the hemolysis of red blood cells by vitamin K. Analogues such as Synkayvite caused occasionally hemolytic anemia in premature infants whose only medication has been prophylactic daily injection of Synkayvite in large doses (>10 mg/day) (23). It has been shown previously (24–28) that red blood cells taken from vitamin E deficient rats are unduly sensitive to hemolysis *in vivo* and *in vitro* to substances such as dialuric acid, H_2O_2. Newborn infants (26) and again especially premature infants (29) have a physiological vitamin E deficiency detectable by the increased susceptibility of red blood cells—even *in vitro*—to H_2O_2. Allison and his collaborators (30) have clearly demonstrated that the hemolysis observed in rats after injection of Synkayvite and a few other vitamin K analogues was seen only in animals with vitamin E deficiency. Hemolysis was prevented by previous administration of vitamin E. It may be assumed that these observations on animals are applicable to human newborn infants.

TABLE 7. COMPOSITION OF HUMAN MILK AND COW'S MILK

	Human Milk	Cow's Milk
	%	%
Protein	1.1	3.5
Lactose	6.6	4.0
Fat	3.5	3.5
Ash	0.2	0.7

The overall problem of protein requirement by man is at present in the forefront of interest and is one of the emotional problems in American pediatrics. One may distinguish two groups: high protein and low protein groups. As emotions go, they are often not based on clearly scientific evidence. In this particular instance the question arises: Is human milk good for a human infant? And it is. It must be.

The chemical composition of human milk and cow's milk (table 7) indicates that the protein content of human milk is only about one-third of that of cow's milk. If we give enough calories—and we know how many calories we should give—then we would give between 2 and 2.5 gm of protein in the form of human milk to a young human infant. This should represent the necessary and probably optimal requirement. 'Optimal' is difficult to define. That is one of the other reasons that no figure for protein was given in the Dietary Allowance Table for infants for the first year

of life (31). In form of cow's milk formulae, often 5–8 gm of protein per kg a day are given, especially to premature infants. This contrasts sharply with the 2–2.5 gm of protein breast-fed infants receive. The question arises: Is perhaps the protein of cow's milk a poor protein? Can it be utilized and assimilated in a manner comparable to the protein of human milk? Professor Platt (London) in recent unpublished studies established the biological value, or perhaps more exactly the net protein utilization, the proportion of ingested protein and protein retained for human milk and cow's milk, and found the difference not remarkable—94.5 for human milk and 81.5 for cow's milk, a difference of about 12%. Thus we have to assume that in the form of cow's milk, about 12% more protein will have to be given than with human milk.

In the light of these and similar considerations, the Committee on Protein Requirements of the Food and Agriculture Organization of the United Nations recommended 2.25 gm of protein of 'high nutritive value,' such as human milk and cow's milk for young infants per kg a day as minimum requirement (32).

We have studied the question of protein requirement also on premature infants but time does not permit me to discuss it in detail. It should suffice to say that even in premature infants on low protein rations, (about 2.5 gm of protein in form of cow's milk/kg/day), the results are perfectly satisfactory and statistically not different from those seen and observed on a high protein diet (6.0–8.0 gm protein/kg/day).

The question of possible late effect of high protein and high calorie feeding is of special and far-reaching interest. This is a crucial question which we cannot answer because nobody has yet followed the whole life of a human infant fed, in infancy, human milk or the present high caloric and high-protein containing cow's milk formulae. I am very much impressed by studies at present going on, and still not completed at the Biochemical Research Foundation in Newark, Delaware, under the direction of Dr. Morris Ross. In this study over 1400 rats were followed over their whole life span. Groups of rats were fed *1*) a commercial 'chow diet' and *2*) semi-synthetic rations with casein as the source of protein in sub-groups *a*) high protein (30%) high carbohydrate, *b*) low protein (8%) high carbohydrate, *c*) high protein low carbohydrate and *d*) low protein low carbohydrate. The fat content in all rations was kept on constant level. Rats with low intake of protein but especially rats with low intake of protein and calories had a greatly reduced mortality rate and increased average life span compared with the rats whose protein intake was high.

They have shown also a significant reduction in the incidence of certain internal diseases (pneumonia, tumors, renal and vascular abnormalities, gastrointestinal afflictions). For example, rats on a high protein (30%) high carbohydrate diet had an incidence of spontaneous tumors of 35%. Rats on a low protein (8%) high carbohydrate diet isocaloric with the previous ration had an incidence of only 10%. In striking contrast to these observations in those rats whose intake of both protein and carbohydrate had been reduced, there was an incidence of spontaneous tumors of less than 1%.

In summary, infant nutrition may be looked upon from two angles. For present practical purposes it has achieved substantial progress over the last fifty years. However, applying the methods, indirect as they are, of modern biochemistry and nutrition, it may be safely stated that infant nutrition is not a closed chapter.

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Nutrition in Childhood and Adolescence

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THE SUBJECT ASSIGNED TO ME is a broad one, a magnificiently broad one indeed. I have half an hour to discuss the problems of nutrition in childhood and adolescence. I am a teacher, a pediatrician, and in the field generally considered defined by the narrower concept of nutrition, I am without research activities. I thus cannot report work of my own and it does not seem profitable for me to undertake to present to you a review in any tabular form of the enormous data related to nutrition that has been collected in the last two decades.

I have chosen to discuss therefore only the problems of nutrition in childhood and adolescence which present themselves most commonly and importantly to the pediatrician, and to outline some of our areas of ignorance, first spending a few moments on certain general principles that concern me.

It seems clear to me that the problems of nutrition in the narrower sense only, regarding what is essential in food elements for good health, what is a poor diet and a good one, can hardly be separated from many other most basic problems of physiology, particularly that most neglected field in children, physiology of digestion. In the past two decades, particularly stimulated by World War II and its after-effects, an enormous amount of data has been accumulated in the study of nutrition by chemical analysis of the blood, tissues and by most elaborate balance studies, and a voluminous collection of normal data has resulted. These have been to a very great extent indeed carried out in children in good health, which was logical, but the pediatrician, caring for children with somatic and psychic disease, in spite of all this work, finds vast numbers of questions still unanswered. It seems that the problem of ideal nutrition in the healthy child, as determined by blood-plasma levels of different elements and by balance studies, which have been so diligently studied, are fundamentally different from the problem of the child in ill health, almost regardless of the nature of the sickness. The data acquired from the study of children in health cannot be simply applied to the problem of children in ill health any more than data on one animal can be easily assumed to apply to another.

In spite of heroic attempts that have been made in the past to define in a practical and simple way good nutrition and malnutrition, these attempts have been for the most part futile and unrewarding. It seems as hard to define malnutrition in a quantitative exact way as it is to define ill health, or sin, or happiness. There is no sum, even of biochemical data, that can be used to define malnutrition in any particular child, certainly no data that are at all practical to acquire. Clinical descriptions of any but the most severely malnourished or the most severely undernourished child are apt to be only non-specific descriptions of a child who is sick, and the terms that are used for such descriptions, lack of energy, listlessness, restlessness, roughness of skin, tension of the skin, shadows under the eyes, etc. can all be nonspecific results of a wide variety of infection, of emotional disturbances, of fatigue alone or other causes of ill health. The symptoms and signs of early malnutrition in fact are nonspecific. Only in a few cases of maximum evidences of disease from specific nutritional defects is there a characteristic clinical picture. I hope we have now stopped discussions of symptoms of 'subclinical' disease, a concept which is basically absurd. I remember at the end of the war, or during it, a list of symptoms and signs of early malnutrition was published that had separate columns of observations that a mother or schoolteacher could make, and other columns that the physician could make, supposedly to give warning of early signs of malnutrition with great emphasis given to vitamin defects.

These were usually pretty unrealistic. I remember one particularly amusing item which was supposed to indicate something or other which was 'inability to sit.' I can imagine the schoolteacher faced with the usual active seven-year-old who would have welcomed the concept that this child needed a specific vitamin to make him quiet. It makes me think of the cartoon in the *New Yorker* once where a tired mother, in front of a counter full of breakfast foods labeled 'Pep,' 'Vim,' and other characteristic terms, asked the clerk, "Haven't you anything that will quiet him down?"

Even without facing the difficulties of defining nutritional problems and dietary needs in sickness, the question now can still be asked whether, in spite of all the data we have, both a minimum and optimum food intake can be devised that will suit any large percentage of our population under the various conditions of emotion and dietary habits, even without disease, that exist in the citizens of this country who live at economic levels as a whole far better than almost any other country. The vast number of studies carried out with particularly accurate chemical techniques and balance studies still leave us with the information that the effects and needs of various food elements are interlocking and interdependent and that one cannot study the one element without rigorous control of all the other food elements involved. We can certainly hope that in sickness we could be given better guidance as to protein needs, but we still are not sure of minimum protein needs in terms of individual amino acids in growing babies or children of any age, to say nothing of being sure of what we should give specifically in sick children with inadequacies of other food elements or total caloric intake.

It seems to me as a pediatrician that there are two areas of ignorance that need most extensive study. One is the influence of emotion and of infection on intestinal function, and the other, the possibility that focal changes in disease represent final cellular damage from nutritional defect. Macy, amongst others, noted sudden incidences of negative nitrogen balances in perfectly healthy children emotionally disturbed. Far grosser evidences of this occur in any study of children in respect to loss of appetite, vomiting, diarrhea, all brought about by pure emotional disturbance, and these not necessarily transitory but in older children existing over long periods.

We can all remember the ancient observations of Walter Cannon on his cat when some of the first x-ray studies of a contrast medium in the gastrointestinal tract were made. The cat's intestinal function as so observed would go along nicely when she was purring and being petted, but on hearing a dog bark there would be a sudden cessation of all gross intestinal function. But even the grossest and commonest observations by our grandparents made it clear to all that emotional disturbances can cause serious reduction in appetite or digestion. The effect on gross digestion of emotional disturbance, both depression and even excitement, is common knowledge, such as the episode of a little girl who goes to the party and has an awfully good time and, without necessarily overeating the things that are supposed to be bad for her, comes home and vomits everything, completely undigested, hours afterwards. I believe we know little about specific nutritional faults that result from emotional disturbances though we are well aware of gross defects. Some knowledge as to how metabolism effects are mediated through emotion would be just about as important to the practice of medicine as an understanding of the cause and the cure of cancer.

It has always seemed to me that we have accepted with little astonishment one of the commonest phenomena in sickness in children which is utterly mysterious. Why is it that a child with otitis media has symptoms of what is glibly but inaccurately called gastroenteritis? What is the connection there that permits pus in the middle ear to cause excessive peristalsis, poor absorption of fluid from the gut or the increased excretion of fluid into it, anorexia, nausea and vomiting. I use otitis media simply as a specific illustration. Fever itself of course is a symptom and can be associated with extraordinarily marked evidences of gastrointestinal dysfunction, but still we haven't a glimmer of an idea as to the relationship of the two.

We are all well acquainted with the cycle of disturbances caused by anorexia that develops from iron-lack anemia, and also the effect of infection in preventing the absorption of iron in attempts to cure iron-lack anemia.

We here deal with one of our commonest vicious cycles in medicine, susceptibility of children with nutritional anemia to infection, anorexia resulting from anemia itself, and also from the infection, bringing further failure of good iron intake and infection preventing the adequate absorption of iron. This sequence is familiar to us and yet I believe we haven't the slightest idea of why it takes place.

An even more difficult field for research has been touched on and we can hope will lead eventually to vastly important results. This is the possibility that there can be specific nutritional defects in certain groups of cells brought about by disease even though total food intake is excellent in all respects; stated otherwise, that many clinical manifestations of disease are due to malnutrition of certain cells, if you please to so use the word malnutrition. Instinctively our clinicians have felt that this must be so as they resort to large doses of the food elements so mysteriously called vitamins in the vague hope that excessive doses will overcome certain localized tissue lacks.

As you all well know, the problems of nutrition in children in most of the United States, at least those that I am familiar with, are rarely related to economic lack of food. Even in economically poor circumstances nutritional disturbances are more often related to an over-abundance than to a shortage of food, and to over-solicitation in the administration of it. The traditional nutritional defects which we used to emphasize so much in our medical teaching have nearly disappeared. It has for years been extremely difficult to find a case of rickets to show to any group of medical students. Scurvy for a time was more common but even that has disappeared. At one time I used to have about 50 cases of scurvy a year to use for teaching. Of these cases, in my own studies, three quarters at least were due not to ignorance and neglect in a gross way, but to specific ignorance perhaps and over-solicitation. They were the results of the mother worrying about allergy to orange juice or of the contamination of orange juice so that she boiled it, ignorance indeed but not the gross ignorance resulting from neglect.

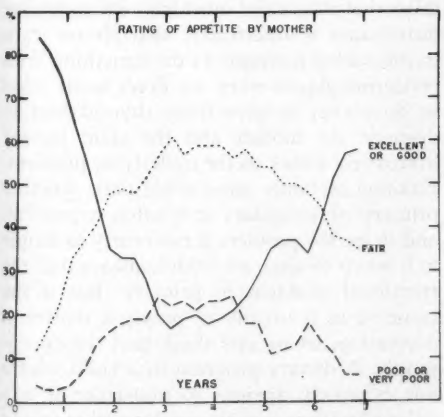

FIG. 1. Percentage of children at each age from 6 months through 7 years whose appetites have been rated as 1) excellent or good, 2) fair or 3) poor or very poor.

What are the problems in nutrition that face us most commonly in children after the infant age? They are quite clearly anorexia at all ages, and obesity. The problems of obesity are most important in adolescence. We see them in younger children too, though most of us still refuse to worry much about it. The problems of anorexia are most common in the young children from 1 year to 6 years, but how much of them are real? Figure 1 shows some data collected by Doctor Virginia Beal (1). Less than 20% of mothers of children between 18 months and 4 years thought their children had a good appetite. Between 50 and 60% thought their children, during this period, had only a fair appetite. They were dissatisfied with their children's food intake.

Although this worry about lack of appetite is often, even usually, not soundly based, it can indeed cause trouble, and serious trouble. The parents can force children to eat and bring about a true loss of appetite on an emotional basis, and a series of events can result which will lead to true malnutrition. It is obvious that we can do a great deal in preventing this. In the first place we must ourselves know the norm. The fact that a child's food intake does not increase much between 10 or 11 months and 4 years of age is not well known. Dietitians and doctors too have overemphasized the balanced diet so the parents think that the child's food

I. *Regulatory Obesity* (No primary metabolic abnormality)
- A. Increased caloric intake
  - 1. "Organic": central nervous system {injury / disease} of hypothalamus
  - 2. "Functional": psychologic
    - Neurotic overeating
    - Non-neurotic overeating (cultural pattern)
- B. Decreased caloric output
  - 1. "Organic": forced immobilization of convalescence
  - 2. "Functional": awkwardness in sports=adolescent day dreaming

II. *Metabolic Obesity*
- A. Neurologic: e.g., lipodystrophy (rare); adiposa dolorosa (rare)
- B. Hormonal: hyperadrenocorticism (rare); adrenal carcinoma
  - hypothyroidism (rare)
- C. Enzymatic: genetic obesity in *mice*, obese-hyperglycemic syndrome

FIG. 2. Types of obesity according to mechanism. (Modified from Van Itallie and Mayer.)

intake at every meal every day has to be balanced.

I believe it is very important to teach young mothers and future doctors that as soon as the infant or the young child begins to show some attempt to put something in his mouth with his hands that this should be encouraged, and a piece of bread, Zweibach, or whatever, can be his spoon or eating implements on which the mother may pile small amounts of solid food. The youngster who smears his face and hair and the floor around his chair with discarded food at 10 months of age, with his mother happily ignoring him for a time, is likely to be the youngster who subsequently offers no great problem of anorexia. We all know from the classic experiments of Clara Davis that given the opportunity, most babies, in health at least, will choose a reasonably balanced diet.

The big problem that faces the pediatricians in our country about nutrition, besides anorexia, is that of obesity and its opposite, extreme under-nutrition. Both of these problems arise more importantly at the beginning and during early adolescence than at any other age. The fat child who is unhappy is perhaps no worse than the fat man or woman who has some unhappiness, but personally I sympathize with it more and think the problem should be more vigorously attacked. I cannot take time to go into a long continued discussion of the fat child and will touch on it only briefly. Sometimes it is hard to believe, though I am certain we must, that obesity is not the result of some profound endocrine disturbance commonly and that it is simply the result of too great a caloric intake for the metabolism of the child. I believe, however, that this has been settled beyond all question by Newburg, though one must admit that there must be great differences in economy of food in different individuals. Figure 2 is a summary by Harry Gordon of the causes of obesity (2). Let me emphasize however that of all the causes he has listed which seem to completely cover the field, the most important is either emotion or X (unknown cause). The tendency of everyone to think that a fat child must have an endocrine disturbance is unfortunate as it always leads to misguided attempts to do something with endocrine glands when we don't know what to do except to give them thyroid and to dissuade the mother and the child himself from direct attack on the underlying problem. Emotion certainly plays a big part; whether primary or secondary it is often a problem and to me the problem is not nearly as simple as it seems to some who think always that the emotional problem in primary. But if the cause is, as it usually is, purely a matter of overeating, let no one think that the cure is simple. A dietary program in a child who is not extremely anxious to undertake it is a serious problem, one almost doomed to failure or, if not to failure, sometimes to the opposite and this is the final point I will make, the causes of extreme malnutrition which we sometimes see in adolescence and which we

like to call anorexia nervosa for want of a better term.

These problems surely belong in the field of the psychiatrist but their preventive aspects certainly belong to the average physician and nutritionist. The causes are varied. One of the causes of severe anorexia nervosa is certainly obesity in adolescence and the ill result of too vigorous attempts or conscientious attempts on the child's part to correct something which had better not have been started. Is there any ill effect of obesity in the infant and of the young child? I am not certain about it. The phenomenon of the 30-pound 8-month-old youngster is now a common one and I have not been convinced by personal observation that over-eating at this age inevitably is related to over-eating at subsequent ages, or to any ill effects at all, except when the mother is worried about the failure of eating in subsequent years following infantile obesity. How soon in childhood should we make efforts to restrict the diet of the obese child? At 8, 10, 12 years, or whatever? Certainly any attempts to reduce the obese child offer all the problems of the reduction of obesity in adults which are indeed very difficult. There are even greater problems because the child must be policed by someone. Until the child himself is eager to lose weight it is extremely difficult and we might say almost next to impossible to police a strict and rigid diet. Attempts at vague reduction in food intakes, cutting out fats, carbohydrates and starches are apt to be futile and worse than futile since they induce the habit of failure as repeated attempts are made that are unsuccessful.

Now, can all these problems be simply answered by the psychiatrist even though in most cases he can find something that to his satisfaction offers an explanation? There is no easy solution for the problem of obesity. We need more information as to whether the habit of over-eating which we condone in infancy and young childhood is in fact a serious one related to over-eating in adolescence. We badly need better clinical techniques for correcting obesity in the ones we now have. Psychiatric aid is expensive, time-consuming, and by no means uniformly successful. Rigid dieting is dangerous as has been pointed out and so far there are no drugs available that make most of us relaxed and contented in their use.

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Nutrition of Children with Congenital Metabolic Disorders

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MY SUBJECT TODAY is "The Nutrition of Children with Metabolic and Congenital Disorders." It is a very broad subject and it gives me an opportunity to select certain better known conditions for this presentation.

In 1909 Garrod (1) described with clarity and remarkable insight a number of clinical entities in which a common factor was some permanent inherited biochemical disorder. He introduced the concept of inborn errors of metabolism. Garrod dealt with such widely different conditions as cystinuria, alkaptonuria, pentosuria and albinism.

With the rapid advances in medicine, biochemistry and genetics, new disorders have been added, and others are knocking on the door awaiting admittance, and perhaps still others remain unrecognized because of our ignorance. A listing of the currently accepted inborn errors of metabolism will be incomplete—for example, the disease that Dr. György mentioned was not on the list I prepared. I am sure a list made today would be considered incomplete tomorrow. It also reveals that all branches of medicine are implicated and includes a variety of specialties, especially pediatrics, dermatology, neurology, nutrition and endocrinology.

That this is an important and timely topic is reflected by the action of the editors of the *American Journal of Medicine* who devoted the May 1957 issue of the Journal to a symposium on Inborn Errors of Metabolism. This issue was ably edited by Dent, who emphasized a concept which is not altogether appreciated, namely, that in dealing with the primary organ involved in the hereditary disease, one must recall that if these diseases are caused by abnormal genes, the basic genetic abnormality must be present from the moment of conception before organ differentiation has occurred and is then passed on to every cell in the fully grown organisms. Thus, it is not correct to say that a certain hereditary disease is due to a primary defect of the renal tubules, whereas it may be correct to say that it is first revealed as an apparently isolated effect. Every other body cell should show this defect, although difficult to detect, because all the cells contain the abnormal genes.

An excellent example of the deliberate search for and discovery of more generalized disorders in hereditary disease of apparently one organ is seen in galactosemia where it has been found that the red blood cells show a metabolic defect similar to that found in the liver (2). As seen in figure 1 the defect occurs in the second reaction where the galactose-1-phosphate cannot be converted into glucose-1-phosphate because of the absence of the transferase enzyme. This is a specific enzyme deficiency which was first found to occur in the liver of children with galactosemia and has recently been found to occur in the red cells of affected individuals.

Variable clinical pictures may be produced in these disorders. For example, the genetic defect may not be directly harmful yet it may predispose the individual to environmental factors which are harmful. The abnormal sensitivity of a constituent of the diet, such as copper in Wilson's disease, galactose in galactosemia, phenylalanine in phenylketonuria may be cited. The clinical manifestations may therefore vary according to the nature of the environment and it is possible by looking into the environmental factors that a lead for therapy may be obtained.

An attempt to arrange the various disorders is made in figures 2, 4, and 7 under the broad heading of carbohydrates, lipids and proteins. Figure 2 lists in addition a few of the

Galactose + ATP→Gal-1-P + ADP (A)
(Galactokinase)

Gal-1-P + UDPG⇌G-1-P + UDPGal (B)
Phospho-galactose-uridyl-transferase

UDPGal⇌UDPG (C)
Galactowaldenase

FIG. 1

Carbohydrates

Pentosuria
Fructosuria
Galactosemia
Diabetes mellitus
Glycogen storage diseases
1. Heart involvement (Pompe)
2. Von Gierke
Complex CHO storage disease (Craig and Uzman)

Endocrine

Goitrous cretinism
Andrenogenital syndrome
Familial hypoparathyroidism
Diabetes insipidus (not all)
Idiopathic hypoglycemia

Others

Familial periodic paralysis
Hypophosphatasia
Porphyrurias
Hypercalcemia (severe form)
Familial hyperbilirubinemia (Crigler-Najjar)
Muscular dystrophies
Vitamin D-resistant rickets
Organicaciduria
Maple syrup syndrome

FIG. 2

endocrinopathies and miscellaneous conditions. If you look through the list you will see that we have included hypophosphatasia and at the very bottom we have maple syrup syndrome, which is a new entity recently described by Menkes *et al.* (3) of the Boston Children's Hospital. This disease is characterized by central nervous system disorder. These children excrete an abnormal chemical compound in their urine, the nature of which is still undetermined. It is a familial disorder and is inherited as a mendelian recessive.

I will speak briefly about galactosemia. The specific disorder in galactosemia is an inability to metabolize galactose in a normal manner. This may result in high galactose blood levels, in deposition of galactose in various tissues and interference with growth. The importance of detecting galactosemia is obvious if we are to save affected infants. In severe cases signs may appear during the first few weeks of life in which vomiting, jaundice, weight loss, enlargement of the liver and cataracts may occur. The infant feeds poorly, becomes lethargic and may have frequent, loose movements. The symptoms may occur in a less fulminating form with feeding difficulties, occasional vomiting, and with retardation of growth.

There is still another form in which the symptoms may be so mild as to remain undetected until a family investigation is carried out, because another member is found to have full-blown manifestations of the disease. These children usually have a dislike for milk. They may have some of the laboratory findings such as the abnormal galactose tolerance test and clinical evidence of liver damage.

The diagnosis of galactosemia may be missed not because it is difficult to establish but because this disease is rare and the diagnosis is often not considered. It may be made by identifying the reducing substance in the urine as galactose either by the osazone test, by the mucic acid test or by paper chromatographic analysis. The galactose tolerance test is always abnormal. A high blood level of galactose follows the oral administration of this substance, which is excreted slowly. Nearly 50% of the ingested galactose can be recovered from the urine. In addition to galactosuria, proteinuria and aminoaciduria are also found. Abnormalities in liver function may be detected, such as the prolongation of the prothrombin time, a rise in serum alkaline phosphatase and in serum bilirubin. The mortality rate is very high in the untreated baby with the severe manifestations of this disease.

The importance of this discussion is to point out that treatment is essentially one of rigid exclusion of all lactose or galactose from the diet. In providing a galactose-free diet one must be aware of the fact that occasionally medicinal tablets may contain lactose as a filler. The rigid exclusion of galactose from the diet should be maintained for a number of years and then perhaps very small amounts of milk or butter may be permitted.

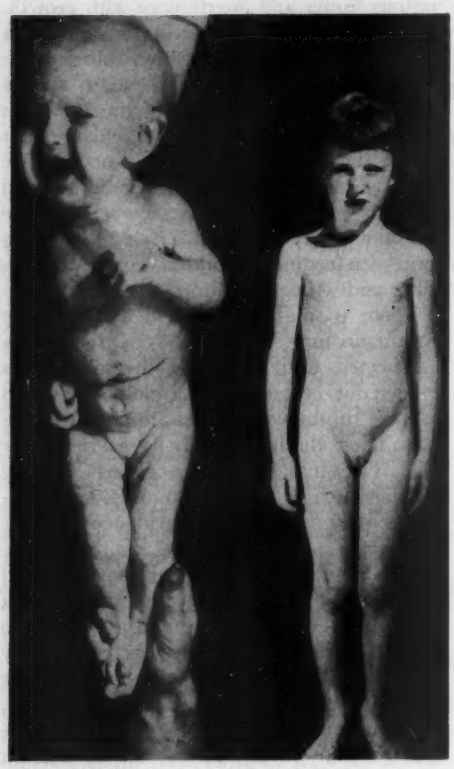

FIG. 3

Lipoid disorders

A. *Xanthomatosis*
   1. Xanthoma tuberosum
   2. Idiopathic familial hyperlipemia
B. *Other lipidosis*
   1. Niemann-Pick
   2. Gaucher's
   3. Tay-Sachs

Amino acids → Protein → Complexes

FIG. 4

The exclusion of galactose from the diet will produce a reversal and often complete clearance of all symptoms, with restoration of normal health. The prognosis, in part, depends upon the severity of the condition, the age at which therapy was begun, perhaps on the strictness of the diet and some unknown factors. It is not an uncommon experience to see cataracts disappear and liver function return to normal following the introduction of a galactose-free diet. One of the late complications is mental deficiency. However, there are a number of youngsters who appear to show normal mental development.

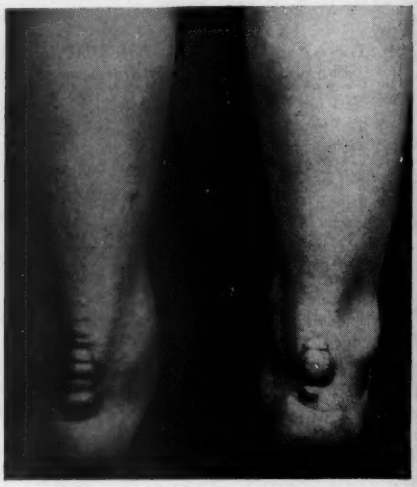

FIG. 5

On the left of figure 3 is a baby 2 months of age with galactosemia. The mark over the abdomen indicates the size of the liver. This child had all the laboratory findings of galactosemia and galactosuria. She was put on a milk-free diet and the picture on the right shows her 7 years later. This girl is now 10 years of age and only recently was found to have cataracts. She had been followed very carefully and we thought she was on a diet free of galactose all of her years. Mentally, she appears average.

I will say very little about lipoid disorders (fig. 4). We have little information as to the nature of the enzymatic defects in these diseases.

Figure 5 illustrates the large nodules in a youngster with xanthoma tuberosum. These children usually succumb in childhood as a result of coronary heart disease. Figure 6 is shown through the courtesy of Dr. Crocker of the Children's Hospital who attempted treatment of a youngster with xanthoma tuberosum. The cholesterol levels are extremely high. This child has been followed for a number of years and you can note the various therapeutic attempts indicated on the bottom right-hand side of the figure. The

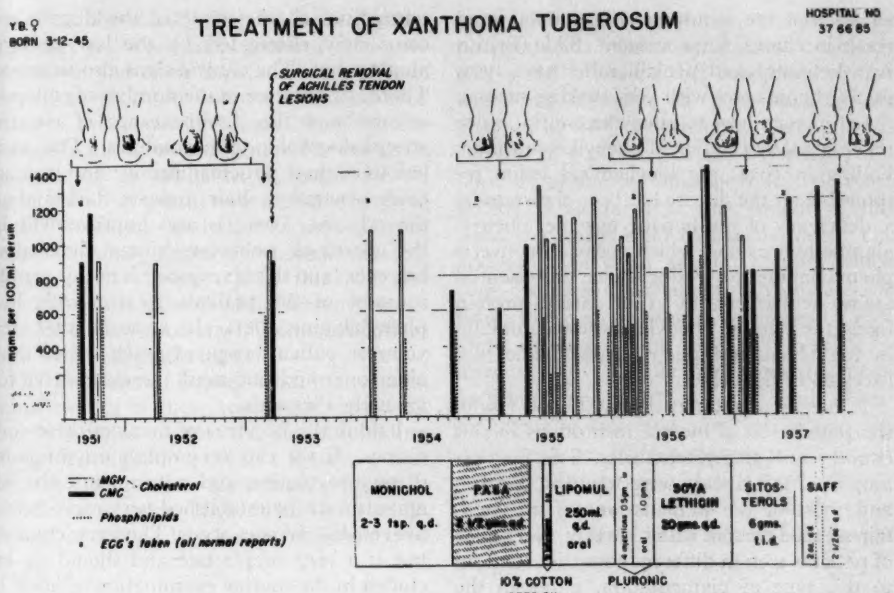

FIG. 6

Aminoacidemia

Phenylketonuria

Aminoacidurias

Cystinuria
Cystine storage disease (lignac-fanconi)
Detoni-Fanconi
Glycinuria
A.A. associated with mental deficiency
Familial tubular glycoaminoaciduria
Alkaptonuria

Peptids

? Celiac disease

Defects in protein synthesis

Agammaglobulinemia
Ceruloplasmin deficiency (Wilson's Disease)
Hemoglobinopathies
Afibrinogenemia
Deficiencies in relation to clotting mechanisms

Mucoprotein

Cystic fibrosis of the pancreas

Collagen + elastic tissue

Osteogenesis imperfecta
Ehlers-Danlos

FIG. 7

course of his disease did not appear to be altered by the various therapeutic efforts. This child died rather suddenly of a coronary occlusion.

In figure 7 I have listed the disorders in which amino acids, proteins and protein complexes are involved. You will note that I have separated phenylketonuria from the other aminoacidurias because in this condition the blood level of phenylalanine is elevated whereas the blood level in the other conditions under discussion is not elevated but the excretion of amino acid is increased.

I will select for discussion phenylketonuria, celiac disease and cystic fibrosis of the pancreas. I might say, in passing, that in Wilson's disease (not Jim Wilson who preceded me but an English neurologist who described this disease many years ago in which neurologic manifestations become apparent, usually beyond the childhood age), it has been shown that in addition to the copper toxicity which these individuals have, there is a deficiency in the production of ceruloplasmin, the protein that carries copper in the blood. The other reason for mentioning this is that the recent use of diets which are very low in copper, with the addition of substances which

will hasten the elimination of copper, may result in clinical improvement. BAL (British Anti-Lewisite) and penicillamine have been used in some cases with very striking success.

Let us turn now to phenylketonuria. Since the original description of phenylketonuria by Folling in 1934, the biochemical lesion responsible for the disease has been shown to be a deficiency of the hepatic enzyme, phenylalanine hydroxylase which normally converts phenylalanine to tyrosine. Since this essential amino acid is present in all natural protein foods, the ingested phenylalanine accumulates in the blood and phenylketone bodies are excreted in the urine.

It has been estimated that about 1% of the population of mental institutions in this country are phenylketonurics. The first examples of this disease were found in Norway and most of the patients were fair-haired, fair-skinned persons with blue eyes. Over 90% of patients seen in different countries conform to this type of pigmentation, although the disease is not limited to people of North European origin. It is clear that the majority of phenylketonuric patients are of low-grade intelligence except possibly during the first few months of life.

The majority of untreated patients are idiots. Perhaps one-half of them never learn to talk and one-third never learn to walk. There are, however, borderline mental defectives, and a very few examples have been reported with only slight mental retardation. The behavior of these children includes finger posturing, minor choreoathetosis, occasionally spastic paraplegia and agitated behavior. Eczema and other skin conditions and epileptic seizures occur in about one-third of the patients and encephalographic abnormalities are found in roughly 80% (4, 5).

The development of a rational therapy for this disease by Bickel (6), Armstrong and Tyler (7) has brought the first glimpse of hope in a disease chiefly characterized by mental deficiency. The phenylalanine-deficient diet has almost uniformly produced results which supports the concept that the disease manifestations are secondary to the accumulation of phenylalanine. It will still require much more time to determine whether complete relief of signs and symptoms can be achieved. The biochemical abnormalities characteristic of the disease are completely eliminated by the low phenylalanine diet. The clinical signs also improve. There is a decrease in the number of epileptic seizures and the disappearance of electroencephalographic abnormalities. The skin lesions of these patients improve and in most cases new-grown hair appears darker than the original. There is also improvement in the neurologic behavior. Mental deficiency, however (and this is very sad) is not reversible in most of the patients treated with low phenylalanine diets. It appears that the younger patients respond much better than older ones and one must therefore strive for an early diagnosis.

I think this is so true of many of these conditions. If we can accomplish anything by dietary regulation and adjustments, the diagnosis must be established very early before irreversible changes occur. The ferric chloride test is a very simple one and should be included in the routine examination of urine in any child who shows developmental retardation. Figure 8 illustrates the ferric chloride test. On the left is a normal urine, slightly acidified. Ferric chloride is added. In the center is the urine of a child who suffers from phenylketonuria, and on the right is the urine from the same child after he had been on a phenylalanine-free diet for a number of months. Note the intense color in the positive test.

In planning therapy, biochemical control should be maintained. When too rapid a depletion of phenylalanine occurs, one may encounter an unexpected danger. A number of fatalities have been reported when blood

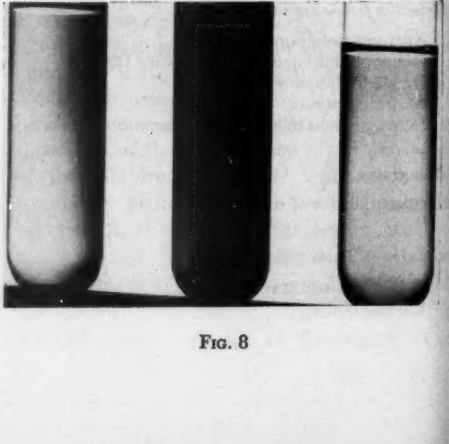

FIG. 8

phenylalanine levels dropped very rapidly. The diet is indeed an unnatural one, very expensive, and often unpalatable. In spite of these drawbacks, the infant who is discovered to have this condition should be given the benefit of this treatment until more definitive information is available. It must be remembered that this diet was introduced about 5 or 6 years ago and that as time goes on refinements may improve at least the acceptability of it. We hope that this will also provide clearer indications for therapy, standards for dietary control with some indications as to what one might expect.

Dr. Richmond Payne, who has studied about twenty of these youngsters, now feels that it is useless to start the diet on children above the age of 4 years. Figure 9 was prepared from one of his treated patients in collaboration with Hsia. This is a child treated at a state hospital in Massachusetts. You will note the very high levels of blood phenylalanine. The normal level is around 4 or 5 mg %. As the diet is adjusted so that decreasing amounts of phenylalanine are given in the diet, the concentration of phenylalanine in the blood drops, the urinary abnormal substances disappear or decrease greatly. Unfortunately, the weight of this youngster suffers if the diet is continued. The addition of a small amount of milk which contains a small increment of phenylalanine brings about an increase in weight and a very slight increase in the blood levels. This illustrates the need for biochemical control for study purposes. It was the result of observations of this kind that led him to the statement that children above 4 probably are not benefited a great deal except perhaps that their behavior and their care is made easier, but so far as their mental accomplish-

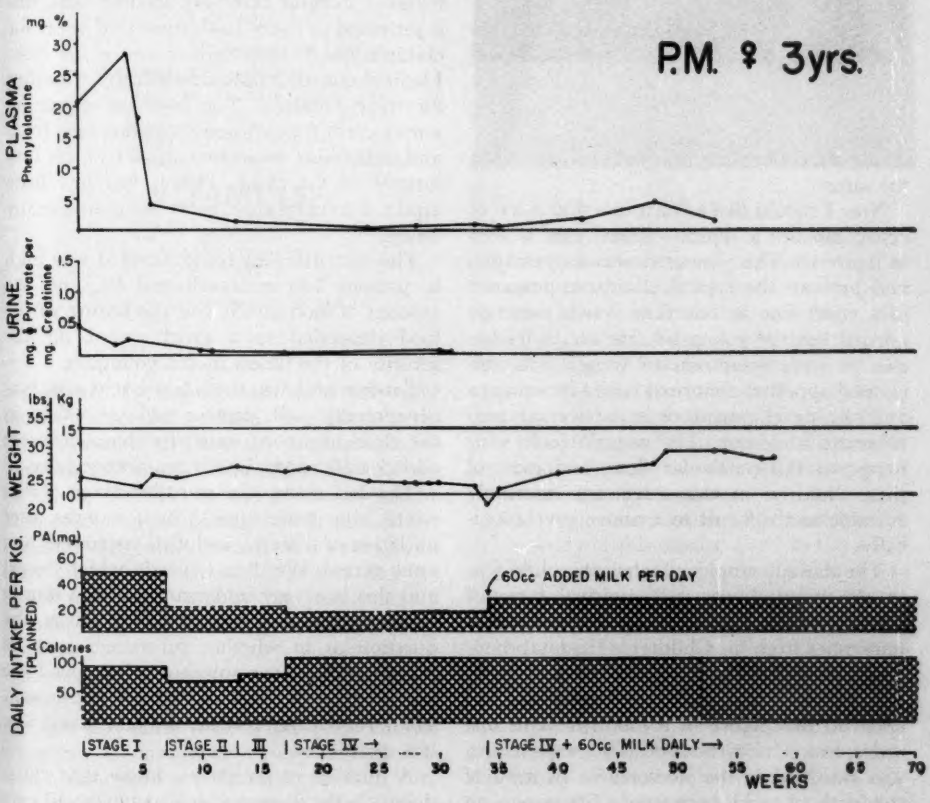

FIG. 9

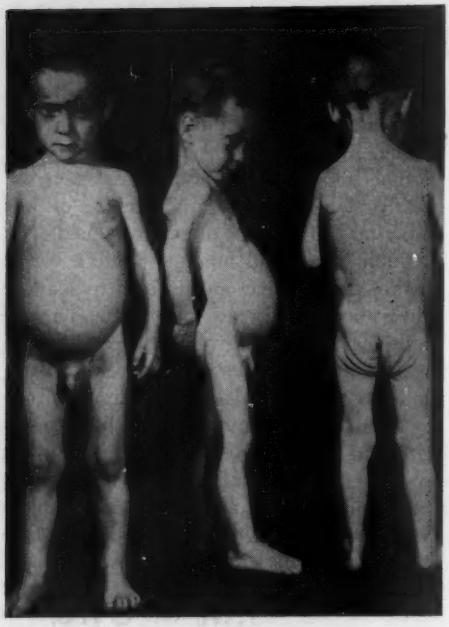

FIG. 10

ments are concerned, they still remain about the same.

Now I should like to turn to a discussion of celiac disease; a typical clinical case is seen in figure 10. This youngster was seen in 1939 and presents the typical clinical appearance of a child who at one time was a perfectly normal healthy youngster. He gradually began to have symptoms of weight loss, decreased appetite, abnormal bowel movements and the development of an abnormal protuberant abdomen. He doesn't look very happy at this particular time, and most of these children at this stage are extremely irritable and difficult to manage psychologically.

The therapy employed when this child was in the hospital was an empirical form of therapy which I am sure Dr. Wilson would remember from his Children's Hospital days, and one which Dr. Blackfan introduced. It was divided into various stages. We will come to that figure in a moment. This disorder, as well as cystic fibrosis of the pancreas, was classified in the steatorrheas in most of the textbooks and there were a few papers on

THERAPY OF IDIOPATHIC CELIAC DISEASE

1. Intelligent nursing care
2. Diet: high in protein, low in carbohydrate and fat with increases in very slow stages
   a) Milk, fat free, 2% lactic acid, protein, etc.
   b) + Bananas, curds, beef, egg, orange juice
   c) + Strained vegetables and fruit + farina
3. Vitamin supplements
   Multivitamins
   Water soluble A & D
   Vitamin K
   Vitamin B complex
4. ? Liver, 'tween', etc.

FIG. 11

congenital steatorrheas which perhaps referred to cystic fibrosis more than to celiac disease.

Figure 11 shows the type of care which the children are given. Let me start with intelligent nursing care. We assume that this is provided in every institution that cares for children but I don't believe that is the case. I believe one must provide a substitute mother for these children. The habit of changing nurses every 8 hours and providing new faces and unfamiliar environment isn't to the best interest of the child. This is just one little aspect of nursing care; there are many, many others.

The diet that was recommended was high in protein, low in starch and fat, and the amount of food added and the nature of the food depended to a great extent on the severity of the illness in the youngster.

Fat-free milk was used, lactic acid milk was occasionally used, protein milk, and then as the child improved somewhat bananas were added, milk curds, beef, eggs, orange juice.

The last stage, the so-called stage 3 diet which may have come 3 or 4 months after initiation of therapy, included vegetables and some cereal. We didn't specify which cereal and this is a very important point. Vitamin supplements were added. There was the question as to whether substances such as intramuscular liver substances improved the nutrition or the welfare of these youngsters. We never felt that it really did and that is why it is questioned.

A number of lay people know that celiac disease is the disease which bananas will cure

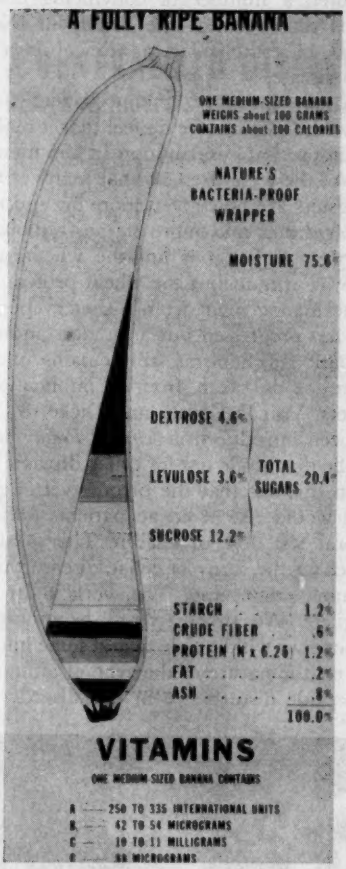

FIG. 12

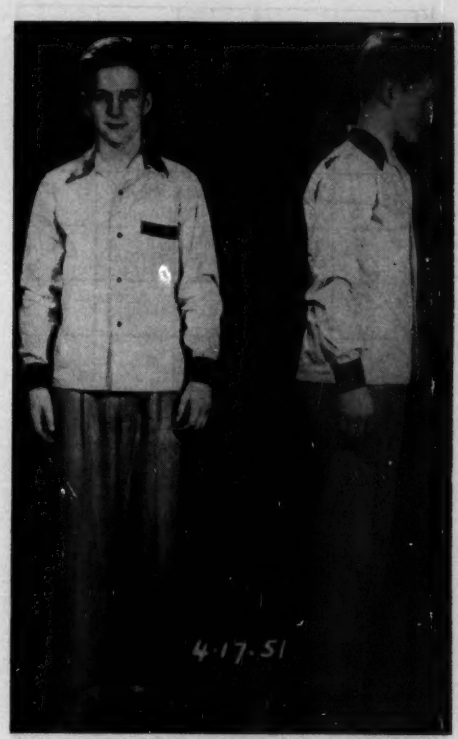

FIG. 13

and figure 12 happens to be a very nice illustration of the banana. I couldn't resist the temptation to show this photograph before this audience. It shows the banana, the nutrients, the calories and it also shows the high concentration of utilizable sugars. Many children with celiac disease were treated with high intake of bananas. Sometimes they received as many as 8 or 10 bananas a day for months on end and this appeared to be very beneficial.

Figure 13 shows the same youngster I showed earlier. He is now about 14 years of age and has made a fairly complete clinical recovery. He has been eating all types of food and no food seems to disagree with him. He leads a perfectly normal life. Not all children who have severe idiopathic celiac disease have this completely reversed clinical picture. Many do, but they still have biochemical abnormalities which may be detected by specific tests. If one does fat absorption studies, one may find, in spite of the excellent clinical appearance, that there may be a defect in fat absorption. There may also be a defect of absorption of glucose from the gastrointestinal mucosa.

One of the most significant advances made in the study of this disease came as the result of a war experience in Holland where it was found that those children with celiac disease who were not able to get bread thrived whereas the other children didn't do quite as well. It was therefore felt that perhaps eliminating wheat from the diet—eliminating bread—would have something to do with celiac disease. The Dutch workers came upon this theory which they have worked on very assiduously for the past 7 or 8 years and have

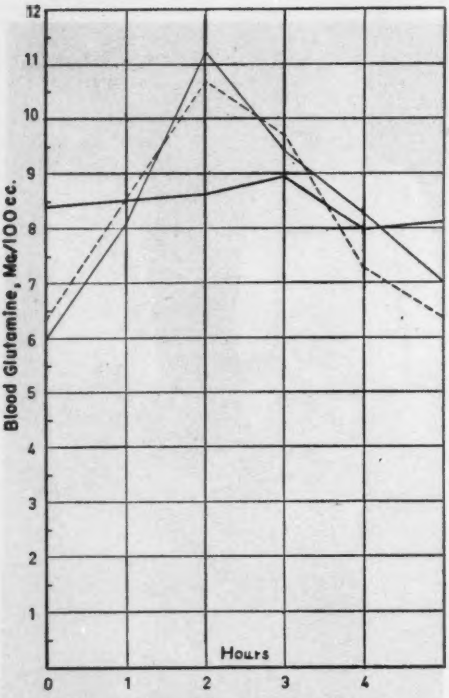

FIG. 14

presented a number of convincing clinical reports that a wheat-free diet is all that is needed in establishing a clinical cure for celiac disease.

Not all of us are convinced that this is always the case but we do feel that it makes a very important contribution in the management of these children, so that many of these youngsters are now given more fat and more carbohydrates and more starch, although it has been shown it is not the wheat starch that was at fault but the wheat protein.

The management from a dietary point of view has progressed but an understanding of the basic mechanisms still remains unclear. Figure 14 is taken from a publication of Weijers, Van DeKamer and Dicke (8). This has been introduced in *Clinical Pediatrics* as a specific diagnostic test for celiac disease. They felt in this test that the blood level of glutamine would rise in celiac patients following an oral test dose of gliadin. This is an approach to the study of celiac disease that we are now attempting. The work is far from complete. We are just really beginning and we hope we will be able to add some information on the nature of the type of amino acid or peptide disturbance in this disorder.

FIG. 15

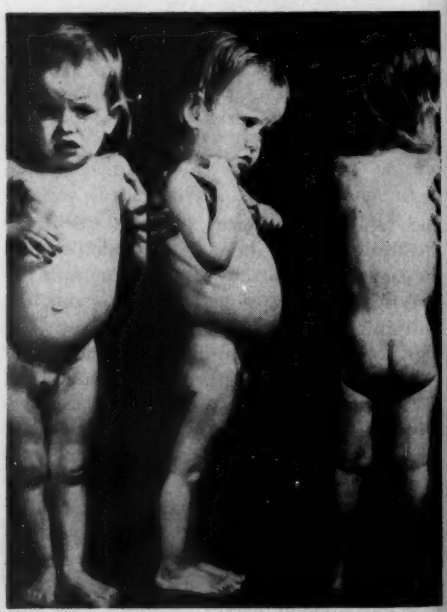

FIG. 16

HEREDITY ... DISTURBANCE OF AUTONOMIC NERVOUS SYSTEM

A GENERALIZED DISEASE
involving mucus secreting glands

VISCID SECRETION AND SMALL DUCT OBSTRUCTION PRODUCES . . . . . .

PANCREATIC INSUFFICIENCY
Before birth – Meconium ileus
After birth – Nutritional failure

PULMONARY CHANGES
Early – Atelectasis and emphysema
Infection [usually staphylococcal]
Bronchitis
Bronchopneumonia
Late – Bronchiectasis

also changes in gall bladder, gastro-intestinal glands, salivary glands, liver etc

FIG. 17

INTESTINAL

Huge appetite
Failure to thrive
Abnormal stools
Poor nutrition
Abdominal distention
Poor fat tolerance
Rectal prolapse

FIG. 18

II. *Indirect*

A. *Metabolic balance:*
Nitrogen and fat intake and output
B. *Stool examination*
(1) Gross examination (see A above)
Excess bulk with increase in total fat and nitrogen
(2) Microscopic examination
Fat
Starch
Proteins (Schmidt Test)
(3) Enzymes—trypsin
C. *Absorption tests*
(1) Fat
(a) Cream
Chylomicron counts
Fatty acids
(b) Vitamin A esters vs alcohol and aldehyde
Serum levels of vitamin A
(2) Proteins
(a) Gelatin or casein absorption tests
(b) I^{131} labelled casein
D. *Clinical response*
(1) To dietary adjustment
(2) To an adequate potent pancreatin preparation

FIG. 19

Figure 15 is the same youngster 6 months apart. This youngster is shown because of a new technique which was introduced relatively recently. What we did in his case was to give him a gluten-free diet and obtain intestinal lumenal biopsies with the parents' permission when therapy was begun and after 6 months when his clinical condition showed marked improvement. We were disappointed to find that the intestinal lumenal biopsies did not reflect the improvement in his clinical condition. The intestinal mucosa in both instances showed a flattening of the epithelium and a reduction in size of the villae. Similar changes have been described in sprue.

I would like to say a few words about cystic fibrosis which I have left to the very end. In coming into this auditorium this morning I noticed that Dr. Dorothy Anderson was here and I am pleased because she was one of the first to call the pediatrician's attention to a syndrome which had formerly been unrecognized. She called this disease cystic fibrosis of the pancreas, in a paper presented in 1938 (9), and since then has continued to make contributions in the study of

FIG. 20

cystic fibrosis. One of her recent studies involves the deficiency of vitamin E in cystic fibrosis (a deficiency for which physicians are unable to find clinical counterparts).

This child shown in fig. 16 first came to our attention because of symptoms which suggested celiac disease. Apparently this wasn't a correct diagnosis because the child had chronic bronchopneumonia. This child differed in many respects from the one we showed before. She died as the result of an extensive pulmonary infection. She had cystic fibrosis of the pancreas. We have now learned that this disease is not a disease of the pancreas but it is a generalized disease. Figure 17 will illustrate what we mean by this. I have classified this disease as a disease involving mucoprotein metabolism. We don't know

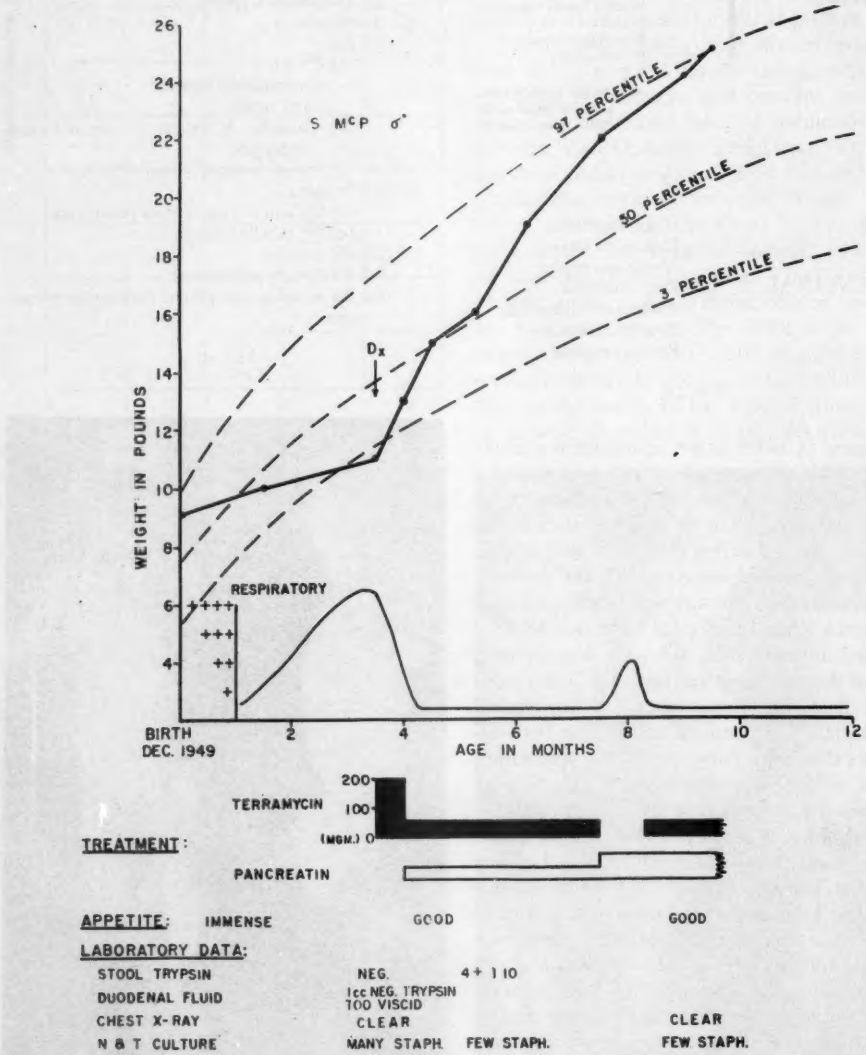

FIG. 21

whether that is the case or not. We don't know how to explain the multiple defects that occur. In addition to the defects that occur here, Dr. diSant'Agnese (10) of Babies' Hospital has demonstrated that there is an abnormality in the excretion of salt in the sweat of children with cystic fibrosis. The quantity of salt excreted in the sweat in this condition is unique. In no other condition in childhood do we encounter it or, for that matter, we know of no other condition where the concentration of salt in the sweat is 3 or 4 times as high as normally occurs in well children or in children ill with a variety of diseases. As a matter of fact, this is of importance because approximately 97% of the children with this disease have this defect. The implications are quite clear. During hot weather or during heat stress these children may develop heat stroke. If one recognizes this, then the application of appropriate therapy will save lives. We have recently had one youngster admitted during the polio epidemic 2 years ago in whom the diagnosis of encephalitis was suspected. In reviewing that youngster's case, he turned out to have cystic fibrosis, which went unrecognized but manifested itself in peculiar central nervous system symptoms secondary to salt loss.

Figure 18 shows the main features of the pancreatic insufficiency symptoms that occur in these children. In spite of the tremendous appetite, these patients fail to gain in weight, they have abnormal stools, they excrete excessive amounts of fat and nitrogen in the stool, the nutrition is impaired. In addition, they may have abdominal distention and rectal prolapse—a symptom which often may be the presenting complaint of the parents. This latter symptom can be controlled by appropriate nutritional therapy.

Therapy consists of administering protein hydrolyzates to the very young babies or pancreatic substitution therapy to permit the hydrolysis of the protein so that amino acids can be produced and absorbed. There is no defect in the absorption of amino acids or glucose but there is a deficiency or defect in the absorption of fat. If the diet is corrected by pancreatic substitution therapy or by the use of amino acid preparations and fat is slightly reduced in the diet, these patients can thrive nutritionally. They also are given two or three times the usual amount of the multi-vitamin preparations.

Approximately 90% or more of the patients with cystic fibrosis develop pulmonary manifestations. These symptoms may begin at any age and lead to pulmonary infection which is the life threatening aspect of cystic fibrosis. We advise the use of antibiotics in the face of pulmonary infection.

Figure 19 shows the type of examination one can do to test pancreatic function. These are classified as indirect tests, the direct referring to the examination of duodenal fluid for enzymes, viscosity and mucoprotein content.

I have a few figures which illustrate therapeutic response. The first one (fig. 20) shows a 3½-month-old baby who came to us in March of 1950. He had typical symptoms of cystic fibrosis. He had cough, a tremendous appetite and failed to gain in weight. His mother was quite frantic when she came to the hospital with this child in the same condition as her first child who died at the age of 9 months. Our patient weighed about 9 pounds at birth and had gained to a little over 11 pounds by the age of 3½ months. He was coughing a great deal—he was up all night with a hacking type of cough. The diagnosis

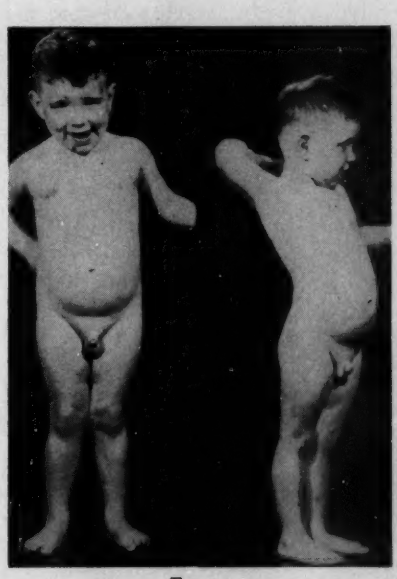

FIG. 22

was established by studying his duodenal fluid, which showed no tryptic activity in 1 ml.

Figure 21 shows his growth response. He was started on terramycin. This was in March 1950 and he was our first patient to receive this antibiotic. His response was dramatic, not only in so far as weight was concerned but also from the point of view of respiratory symptoms. We later added pancreatin. We were rather pleased that the terramycin permitted growth and improved the infection. I would like to point out one therapeutic problem. We continued the terramycin for some time and then decided to stop it. The respiratory symptoms recurred, and we felt that it would be much wiser to continue with a minimum dose of terramycin or 50 mg a day. At that time this dose was considered a very infinitesimal dose. Apparently this was enough to control the pulmonary infection. Figure 22 is a plate taken when this patient was 3½ years of age.

This disease was formerly considered uniformly fatal. With early diagnosis and the establishment of therapy, it is now possible to maintain many of these children in a satisfactory state of health (11, 12). We now have a fairly large number of patients who are in their adolescent age and a few are married.

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An excellent book, *Inborn Errors of Metabolism* by David Yi-Yung Hsia (The Year Book Pub., Chicago 1959) appeared after the above paper was presented.

NUTRITION AND HEALTH PROBLEMS IN MIDDLE AGE

Introduction

W. HENRY SEBRELL, JR.

Columbia University

THE SUBJECT of our session this afternoon is "Nutrition and Health Problems in Middle Age." I want to open this session with a few remarks about our population. It is estimated that this week the population of the United States will pass the 175 million mark. The forecast for 1980 is that there will be an increase of 90 million people over the population today. The forecasts of the population of the United States for 1980 vary from about 235 million to 270 million. In 1940 the population forecast for 1958 was 149 million, but we actually have 175 million. Thus the birth rate far exceeded what had been anticipated in 1940. In 1957 it was almost exactly double what it was in 1935, so that in about twenty-three years we have about doubled the birth rate in this country; for the first time since 1810 the median age of the population has begun to move toward a younger age. Although we can anticipate a younger population, we have not yet succeeded in doing much about lengthening the life expectancy of our middle-aged people. We now have about 65 million people under 20 years of age. In 1980 we will have about 110 million if the present forecasts hold. In the middle-aged group of 35–64 years we have about 60 million now but we will have only about 70 million in 1980 which will very nearly double the number of people under 20 years of age but will only increase the 35–64 year old group by about 10 million. These figures emphasize the great importance of our program today.

Pathogenesis of Atherosclerosis and Myocardial Infarction

W. STANLEY HARTROFT, ROBERT M. O'NEAL AND WILBUR A. THOMAS

Washington University Medical School

ALTHOUGH IN THIS PAPER the etiology and pathogenesis of atherosclerosis will not be reviewed because several excellent and recent summaries are readily available (1, 2), certain features of coronary arterial disease and its complications as seen in man will be emphasized by way of introduction. A number of experiments conducted in this laboratory that were prompted by these features will be recounted with particular emphasis on the distinction between changes in the vessel wall per se and complications of the latter because the two (the disease of atheroma vs. its complications) may not necessarily be of the same etiology or pathogenesis. We believe that certain points brought out by the production of myocardial infarction in rats by dietary means alone, achieved some two years ago in our laboratories, support the dual concept. Some of these experiments have been generously supported by the Nutrition Foundation and we are grateful to both it and its member-companies for their encouragement.

CORONARY VASCULAR DISEASE AND MYOCARDIAL INFARCTION IN MAN

Myocardial infarction in man (fig. 1) is most frequently an end-result of sudden occlusion by a thrombus filling the lumen of a major coronary artery. Formation of the obstructing clot usually develops at a point on the vessel wall at which pathologic changes of longer duration have been produced by atheromatous disease. But occlusive thrombosis with infarction is not an essential stage of atheromatous disease—albeit a frequent although by no means constant, extension or complication. It is, of course, quite likely that atheroma may act as the localizing and precipitating factor in thrombotic occlusion once the stage for abnormal, persistent intravascular coagulation has been set, systemically. With this distinction in mind, one is less likely to confuse factors important in the pathogenesis of atheroma with other factors, perhaps quite distinct, that are important in the pathogenesis of thrombotic occlusion.

Our approach has therefore been that shown in figure 2. Our hypothesis conceives that for the final production of a myocardial infarct two groups of factors have been at work; one group being responsible for the production of atheromatous changes within vessel walls and the second group responsible for disturbances in coagulation and fibrinolysis. As a result, the first group (atherogenic) are local in action and thereby determine the sites at which the second systemic group (thrombogenic) precipitate occlusive thromboses and infarction.

Before proceeding to some of the experimental approaches suggested by this hypothesis, it is pertinent to look at the anatomical changes found in myocardial infarction in man. In a typical obstructed coronary artery (fig. 3), the lumen is completely filled with organizing thrombotic material. The wall at this point is distorted and thickened by a plaque containing fibrous tissue and lipid, but the lipid is by no means the only component of the lesions; it is often the least important quantitatively depending on the stage examined. The nature of the lipid is however of interest and some of it per se is pathologic. In a composite photograph (fig. 4) three large classes of fats are demonstrated. In a frozen section stained with Oil red O (left half of fig. 4) all fat is retained and by photographing it through crossed Nicol prisms, the anisotropic cholesterol component is demonstrated. Here (and it is representative) the cholesterol is less in amount than that of the rest of the lipid. This section was then passed through alcohol and ether to extract all the organically soluble

FIG. 1. An old infarct of the apex of a human heart with an overlying mural thrombus.

PATHOGENESIS OF
ARTERIAL THROMBOSIS

Local Factor
(Arteriosclerosis)
+
Hematological Factor
(Antifibrinolytic or/and
procoagulative)
↓
Arterial Thrombosis

FIG. 2

fat. It was then restained with Oil red O and it is apparent (right half of fig. 4) that considerable amounts of material that react with the fat-stain have remained. This material is the insoluble lipid to which our

FIG. 3. A typical obstructed coronary artery, its lumen occupied by an organizing thrombus. Hematoxylin and eosin.

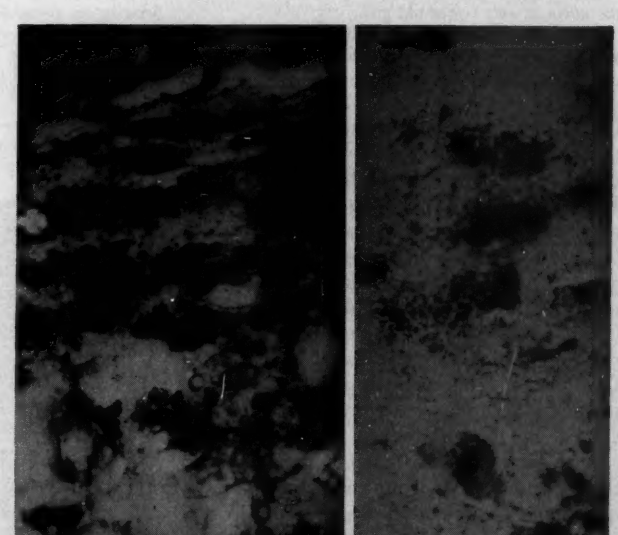

FIG. 4. Photomicrograph of a human arteriosclerotic plaque. On the *left* is a frozen section stained with Oil red O and photographed through crossed Nicol prisms; on the *right* is the same area after alcohol-ether extraction of lipid, the dark material remaining being ceroid.

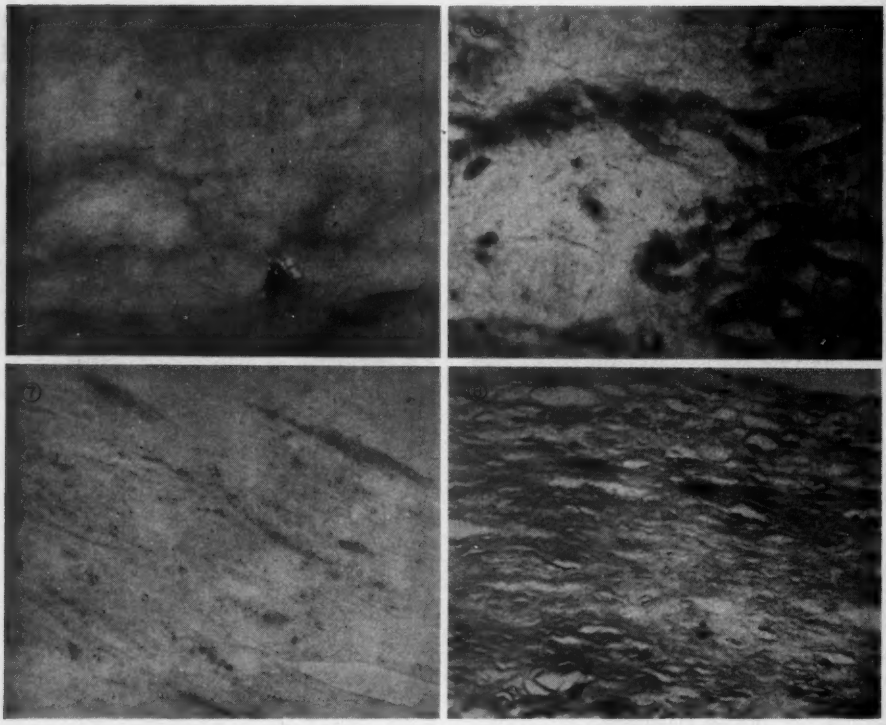

FIG. 5 Gross photograph of the intimal surface of the aorta in an 11-year-old girl.

FIG. 6. Photomicrograph of superficial portions of an atheroma from the aorta in fig. 5. Oil red O.

FIG. 7. The dark granules represent deposits of iron in an aortic lesion. Prussian blue stain.

FIG. 8. Photomicrograph of a 'pearly plaque,' showing the dense fibrous tissue which is the principal component of the lesion.

Chairman Dr. Sebrell and his colleagues gave the name 'ceroid' (3), when they first encountered it in livers of choline-deficient rats. From their work and others we know that it represents a pathologic autoxidation product of unsaturated fats (4). This reaction is not generally recognized by biochemists as one occurring frequently in biologic systems but is well known to paint-chemists. It is the reaction that occurs in linseed oil-paints as they dry, making them resistant to organic solvents. A similar reaction is probably involved in the production of rancidity in certain fats. Emphasis has not been given to the fact however that an analogous reaction, under pathologic conditions, may progress *in vivo* and we have shown that atheromatous plaques are a popular site for the formation of ceroid pigment (5).

Grossly, in the early stages particularly,

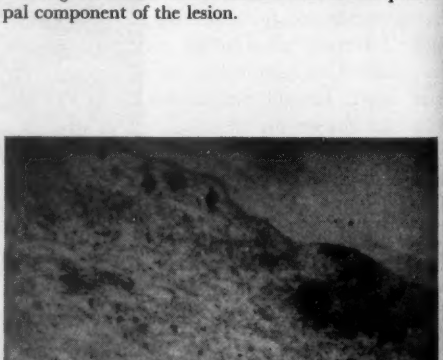

FIG. 9. A layer of coagulated plasma overlies the aortic lesion. Oil red O.

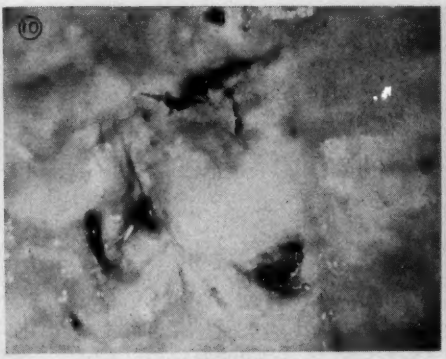

FIG. 10. Gross photograph of the intimal surface of an aorta from an older individual.

FIG. 11. Layering of fat and fibrous tissue in a lesion from the aorta shown in fig. 10. Oil red O.

GEOGRAPHIC DATA

Incidence of pulmonary thromboembolism among 841 autopsied Ugandans 40 to 100 years of age	2%
Incidence of myocardial infarction in same group	0.1%

FIG. 12

the lipid component of atheromatous plaques is prominent, giving a yellow color to the lesions which are frequently called fatty streaks at this stage (fig. 5). As the lipid component decreases and becomes replaced by fibrous tissue the term 'pearly plaque' has been suggested by Holman and others (6). The photomicrographs to follow were prepared from sections selected from the area shown in figure 5. These lesions were present in the aorta of a young girl, 11 years of age, and therefore we presume may represent early stages of atheroma.

In superficial portions of the lesion one may encounter strands of fibrin encrusted with stainable lipid in suitable preparations (frozen section stained with Oil red O) (fig. 6). Histochemical preparations from similar areas reveal the presence of iron deposits (Prussian blue reaction) (fig. 7). The latter have recently been emphasized by Paterson in Canada (7), indicating that components of the blood stream may play an important role in building up the deposits of atheroma. The fibrin and fatty strands shown in the preceding figure would also support this concept. I shall return to this hypothesis.

Sections from the pearly plaques reveal much less lipid, most of the material representing fibrous tissue and perhaps fibrin (fig. 8). Frequently a layer of coagulated plasma overlays the surface of the plaque (fig. 9). This feature is seen only in frozen sections, because during the processing of paraffin sections the layer shrinks and contracts so that it is no longer readily apparent.

By way of contrast, larger lesions in older individuals (fig. 10) are frequently ulcerated and encrusted with calcium deposits. Here one frequently observes microscopically that stratification is a prominent feature (fig. 11) with layers of stainable fat and ceroid interposed between layers of fibrous tissue. This appearance irresistibly suggests that a succession of acute events may have occurred over the years, building up fat and fibrous deposits alternately in a manner analogous to the rings of the bark of a tree. Perhaps one day, the informed pathologist will be able to decipher from such a picture the nutritional history of the individual.

A great deal of attention has recently been focused upon the geographic pathology of atheroma and myocardial infarction. Space will not permit a recapitulation of these advances, but I will touch on certain aspects of this subject that have interested us. Myocardial infarction in Africans is rare (Uganda). If the hypothesis set forth earlier in these pages is correct, that the factors controlling coagulation and fibrinolysis are abnormally altered in patients dying of occlusive thrombosis of the coronary arteries, one would expect thrombotic phenomena elsewhere in the

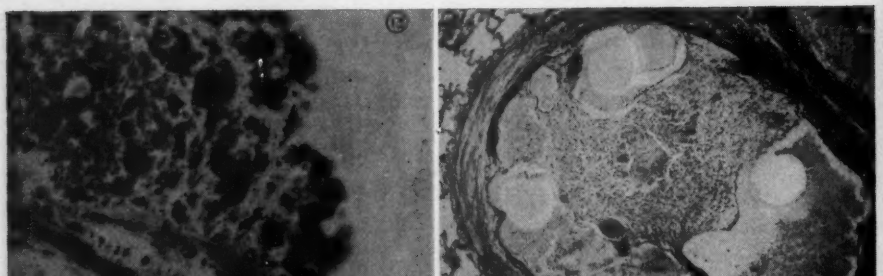

FIG. 13. Cholesterol-induced atheroma of a rabbit's aorta stained with Oil red O.

FIG. 14. An organizing, recanalized thrombus in a large pulmonary artery of a rabbit given intravenous blood clots.

FIG. 15. An eccentric fibrous intimal plaque in a large pulmonary artery of a rabbit, killed after 6 weekly intravenous injections of blood clots.

FIG. 16. Same as fig. 15, showing the varying forms of fibrous intimal lesions encountered.

body to be correspondingly low in populations in which heart disease is rare. As presented in figure 12, amongst the Bantus in Uganda[1] this prediction proved true. Not only is myocardial infarction rare, but thromboembolic phenomena in lungs, legs and elsewhere are only about one-tenth the incidence encountered in the United States where myocardial infarction is also, of course, much commoner. Thus the low incidence of thrombosis in these African people is peculiar not only to their coronary arteries but also to vessels (both arteries and veins) elsewhere in their bodies.

The low incidence of myocardial infarction in Negroes in Africa has been carried over to lesser degree to their descendants here in the United States. Studies of the incidence of myocardial infarction amongst Negroes in St. Louis, New Orleans and Washington, D. C. (8) established that its incidence in the colored was only one-fourth to one-half that in similar groups of white people of comparable age, sex and weight. Differences in dietary habits between these two groups of Americans (white and colored) might be responsible at least in part for the relative immunity of the Negro to heart disease. We are surveying this possibility in St. Louis using appropriately selected groups of each race to elucidate the problem.

[1] These data were obtained by Dr. Thomas on a visit to East Africa, through the courtesy of Dr. J. N. P. Davies, from the files of the Department of Pathology, Makerere Medical College, Kampala, Uganda.

VASCULAR DISEASE AND MYOCARDIAL INFARCTION IN EXPERIMENTAL ANIMALS

Since Anitschkow started his famous experiments more than half a century ago, thousands of plaques have been produced in

experimental animals by either feeding cholesterol or some variant of the cholesterol regimen. But in the literature there are very few reports of any of the animals developing occlusive arterial thrombosis with infarction of the heart or other organs, fatal or otherwise. This fact, I am sure, is known to all of you, but it impressed itself upon me when I was required to review the subject of experimental atheroma in connection with a report to the Council on Food and Nutrition. Dr. Thomas and I agreed to attempt to produce the disease in experimental animals and to see if at least a few might not die of myocardial infarcts.

Our background for this attempt will be presented briefly. Cholesterol-induced atheroma (fig. 13) in a rabbit produces some alterations of the media, but most of the fat is localized in prominent plaques arising from the surface and covered by endothelium. They are filled with foam cells which contain stainable lipid, much of it cholesterol. The foam cell in the human lesion is difficult to find, but they are present in abundance in the rabbit. This does not seem to lead to occlusive arterial thrombosis in animals in more than rare instances at best.

Another counterpart or facsimile of arterial atheroma that can be produced by a completely different method is by injecting preformed thrombi into the ear vein of the animal, in this case the rabbit. The clots are entrapped in arteries of the pulmonary circulation and cause partial or complete occlusion, as you see here. This method was devised recently by investigators in England (9). These organized thrombi (fig. 14) narrow the lumen of the vessel and the thrombus often at one side becomes organized and converted into a thickened fibrous intimal plaque. It resembles atheroma in man in every detail except that not much lipid is present in these lesions (figs. 15 and 16).

Little fat is present in these lesions (fig. 16), therefore, it was decided to combine the injections of clots with feeding various amounts of fats (10), the intent being to incorporate fat into the lesions histologically if possible. This did happen, but of far more interest was what happened accidentally. When one combined the clot injection with stomach-meals of butter in rabbits, the incidence of severe lesions was 80%. The same happened with oleomargarine. When corn oil or sugar solutions were used in isocaloric amounts with the injections of standard amounts of clot, the incidence of lesions in each case was only 40%—approximately half (11). Feeding highly saturated fat with injection of thrombi resulted in their persistence in larger numbers in the lungs of these animals; presumably, the feeding of saturated fat had interfered with fibrinolysis, the mechanism which dissolves thrombi in the healthy animal. Feeding butter and margarine without in-

TABLE 1. SUMMARY OF NUMBER AND PERCENTAGE OF RABBITS IN VARIOUS CORRESPONDING GROUPS REPORTED IN THIS AND IN PREVIOUS EXPERIMENTS WITH 'MODERATE' OR 'SEVERE' FIBROUS INTIMAL THICKENING OF THEIR SMALL PULMONARY ARTERIES

Groups*	Total No. in Group	No. with Moderate or Severe Lesions	Percentage with Moderate or Severe Lesions
Clot-butter	25	20	80
Clot-oleomargarine	12	9	75
Clot-corn oil	15	6	40
Clot-water	15	6	40
Clot-sugar solution	10	4	40
Saline*-butter	4	0	0
Saline*-oleomargarine	4	0	0
Untreated	25	0	0

* Clot suspension or saline given intravenously in each instance and fat or water or a sugar solution introduced into the stomach as described in the text.

TABLE 2. AVERAGE CLOT-LYSIS TIMES (STREPTOKINASE METHOD) FOR SEVERAL GROUPS OF RABBITS GIVEN SINGLE MEALS OF BUTTER, CORN OIL, COCONUT OIL OR WATER

Type of Meal	No. of Animals in Group	Av. Lysis Times (min.)	S.E. of Mean
Butter	31	22.0	1.47
Water	23	15.0	1.53
Corn oil	16	15.5	2.63
Coconut oil	22	13.0	1.62

Av. lysis time for the group fed butter is significantly longer than that for any other group. Differences in lysis time among the other groups are not statistically significant.

TABLE 3. DIET

Casein	20	Thiouracil	0.3
Sucrose	20.7	Choline chloride	1
Butter	40	Celluflour	5
Cholesterol	5	Salt mixture	4
Sodium cholate	2	Vitamin mixture	2

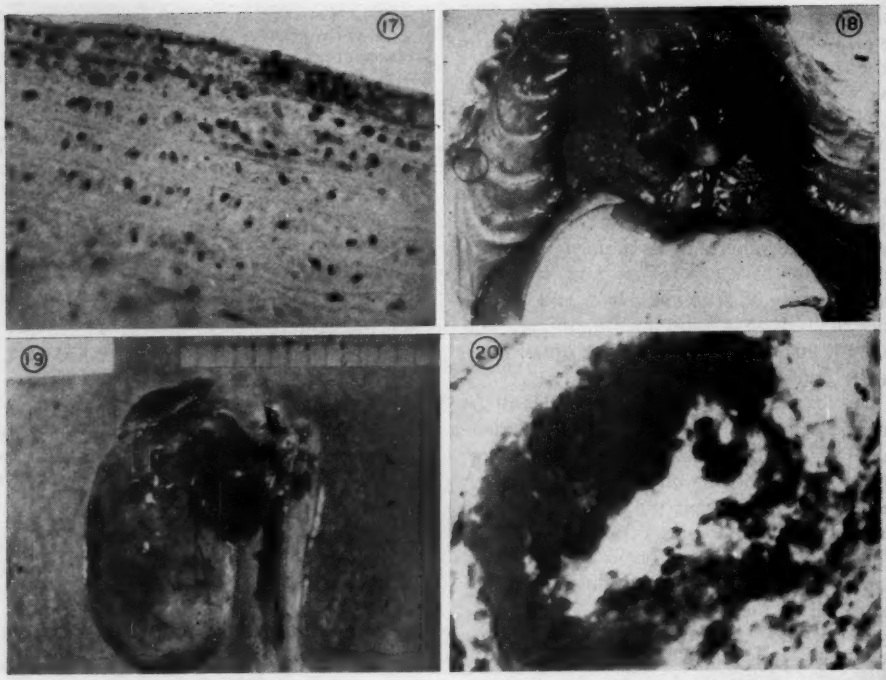

FIG. 17. The granular black material is lipid deposited in the superficial portion of the media of a rat's aorta. Oil red O.

FIG. 18. Apical infarct of a rat's heart seen as a pale, well-defined area.

FIG. 19. Larger infarct involving almost the entire lateral wall of the left ventricle in a rat.

FIG. 20. A small artery in the myocardium of a rat, its wall occupied by extensive lipid deposits. Oil red O.

jecting the clot did not produce lesions, as you would expect (table 1).

By giving these same fats in a single stomach-feeding to a rabbit, withdrawing his blood 3 hours later during post-absorptive lipemia and measuring the rate of clot lysis *in vitro*, using streptokinase to activate it, it was demonstrated that the average clot lysis time was prolonged after feeding butter but was not after feeding the syrup or corn oil or even cocoanut oil (12). It was not a mere matter of saturation of the fat then (table 2).

This test has also been modified for purely *in vitro* studies applied to a large number of substances. By and large, the rule holds, though, that the saturated animal fats prolong clot lysis much longer than anything else.

We thought we had learned how to influence by dietary means the persistence of thrombi in the living animal. We knew from Drs. Hegsted and Stare's work (13) how to produce local damage in the vessel wall of rats by feeding them cholesterol, thiouracil and sodium cholate. We thought if a thrombus would start to form at the site of the Stare-Hegsted lesion, in animals fed a large amount of saturated fat that lysis of this clot might be sufficiently inhibited, that it would become occlusive producing fatal or near fatal myocardial infarction.

The diets which we employed were derived accordingly (table 3). They contain hypercholesterolemic agents used with great success by Dr. Stare and his group earlier in producing plaques, with saturated fat added to favor the persistence of thrombi if they would form. After feeding the diet for 3 or 4 months we met with success sooner than we had anticipated. We had thought it would take a year or two.

In the aortas (fig. 17) the stage of the lesion reached only that of deposition of lipids. But prior to the stage of plaque formation some of these animals died with myocardial infarction. I emphasize this point be-

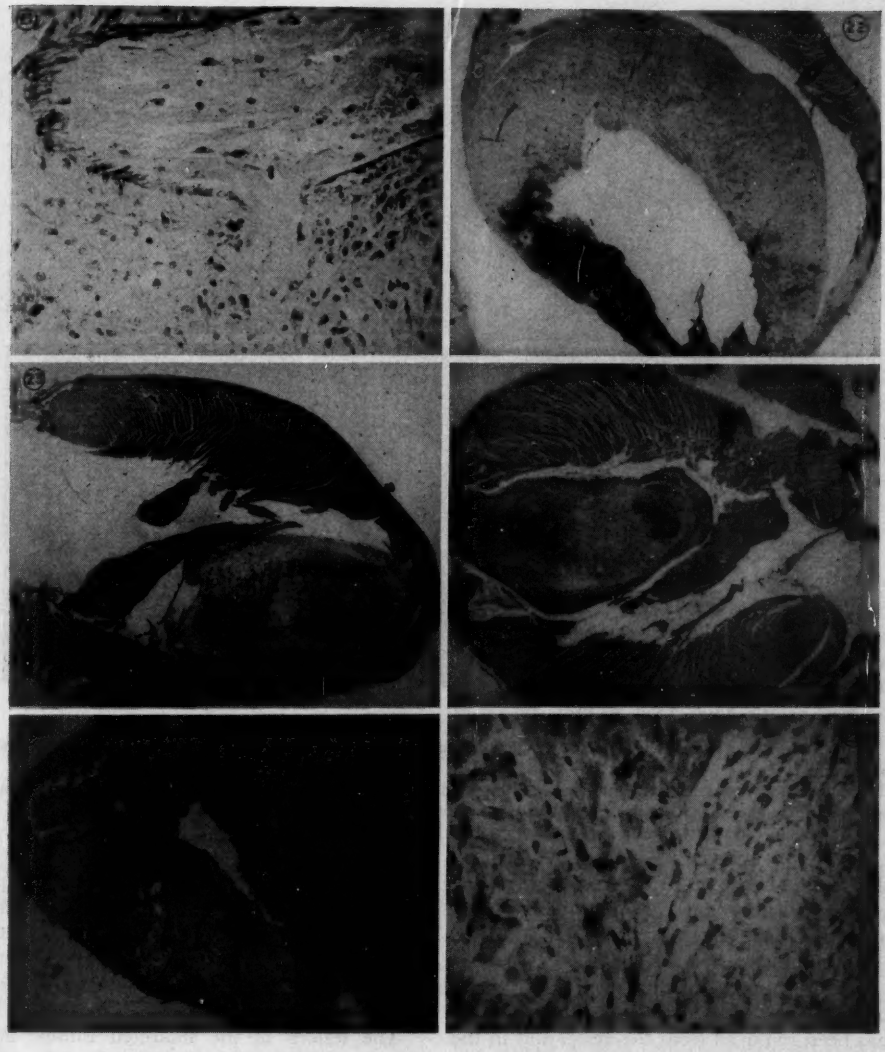

FIG. 21. A large artery occupied by an organizing thrombus. The arterial wall appears normal, but fat has been removed in tissue preparation. Aldehyde fuchsin–van Gieson-hematoxylin.

FIG. 22. A low power micrograph of an infarct of the left ventricle in a rat. The extent of the infarct is shown best by the presence of fat, shown as black. Oil red O.

FIG. 23. Same as fig. 22, with a large mural thrombus occupying almost the entire left ventricle. Oil red O.

FIG. 24. Another infarct, confined to the apex, with an overlying mural thrombus. Aldehyde fuchsin–van Gieson-hematoxylin.

FIG. 25. An organizing mural thrombus practically filling the left atrium. Aldehyde fuchsin–van Gieson-hematoxylin.

FIG. 26. A myocardial infarct in one of the rats showing the sharp line of demarcation between normal muscle on the *left* and the infarcted tissue on the *right*. Aldehyde fuchsin–van Gieson-hematoxylin.

cause the presence of a plaque apparently is not necessary to stimulate thrombotic occlusion, a surprise to us, but it appears to be the fact. We have confirmed this sequence many times (14–16). An infarct in one of these animals' hearts is shown in figure 18. It is the yellowish white area at the apex. This regimen also induces a very fatty liver of the cholesterol type (17). A much larger infarct involving almost the entire left ventricle is

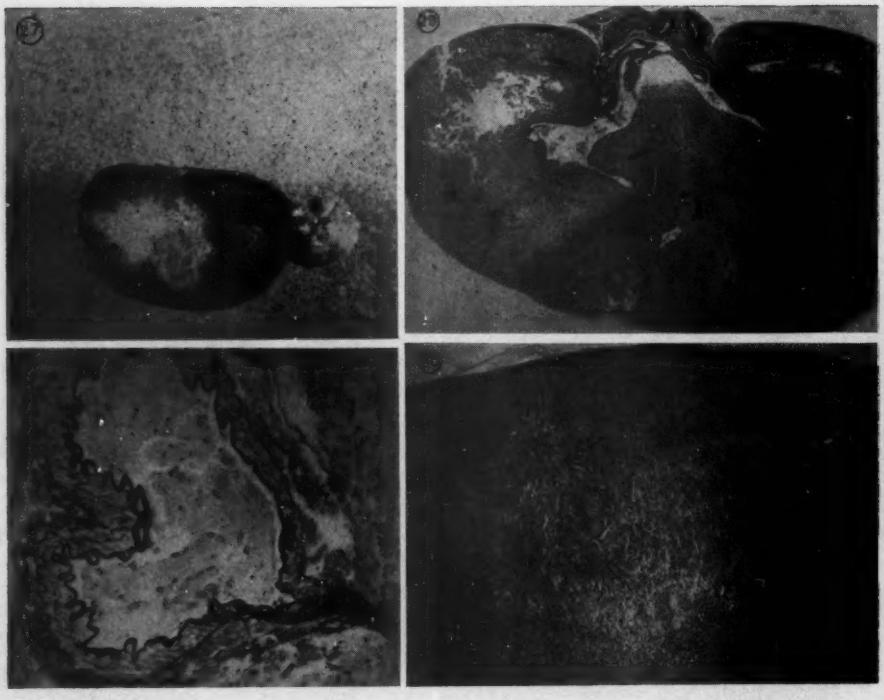

FIG. 27. Gross picture of a large renal infarct with depressed surface.

FIG. 28. A large renal artery occluded by an organizing thrombus. Aldehyde fuchsin–van Giesonhematoxylin.

FIG. 29. One pole of the kidney is infarcted and the renal artery containing an occlusive thrombus can be seen at the hilus. Aldehyde fuchsin–van Gieson-hematoxylin.

FIG. 30. A recent, wedge-shaped, renal infarct. Hematoxylin and eosin.

shown in figure 19. Microscopically, the coronary arteries are usually loaded with abnormal lipid (fig. 20), present in all coats —intima, media and adventitia.

But there are no plaques even at the site of occlusive thrombosis (fig. 21). Abnormal fat has been removed from the vessel and in the preparation of this specimen but the thrombus formed at the site of lipidosis of the wall. In the figure the thrombus is extending into a branch of the main artery.

Photomicrographs taken at low powers of these hearts show the infarcts involving the anterior wall of the left ventricle, the apex and portions of the interventricular septum (fig. 22). They are common sites, of course, in man. Very frequently at the sites of the infarcted or dead muscle large thrombi will form in the left ventricle (fig. 23) similar to the figure in man shown at the beginning of the talk. Sometimes those thrombi will appear to completely fill the left ventricle and I am sure contribute to the animal's death (fig. 24). They may form also in the atrium perhaps by a process of extension (fig. 25), or as a result of fibrillation.

The lesions of the infarcted muscle are sharply delineated and contrast with relatively normal muscle at the edges (fig. 26). This point emphasized that they are on a vascular basis with a sharply demarcated focal distribution. They are not the so-called metabolic muscle lesions associated with potassium excess or other types of dietary abnormalities. Lipid is prominent in these infarcted areas (fig. 22) and small amounts of cholesterol are also found at these sites.

We cannot control the sites at which the infarcts form and they are also found in the kidneys (fig. 27) where they may be large.

TABLE 4. PLASMA CHOLESTEROL, MG %

No cholesterol or thiouracil	84
No cholesterol	158
No thiouracil	540
Total diet 1 mo.	1910
3 mo.	3064

TABLE 5. CHOLESTEROL LEVELS (EXAMPLES IN MG %)

1. Butter, etc.	2335
2. Crisco, etc.	1638
3. Butter, etc. & saltmix	3610
4. Corn oil, etc.	603
5. No thiouracil but butter, cholesterol & much bile salts	4250

TABLE 6. SUMMARY OF RESULTS TO DATE

1. Among 178 rats fed cholesterol-thiouracil-butter 45 (25%) had infarcts.
2. Among 175 rats fed 14 other infarct producing diets 28 (16%) had infarcts.

THEORETICAL BASIS FOR PRODUCTION OF THROMBOSIS IN OUR RATS

Local Factor
+
Hematologic Factor
↓
Arterial Thrombosis

FIG. 31

The renal artery in these contains an organizing thrombus (fig. 28). Again the wall is structurally normal; but in frozen sections it is loaded with fat. The infarcts are in the region of the vascular distribution of the obstructed parent vessel (fig. 29). By conventional hematoxylin and eosin techniques (fig. 30) the typical wedge-shape of the infarct, the ghost outlines of tubules and glomeruli and a zone of reaction at the edges are all in evidence as in similar lesions in man.

We measured plasma cholesterols (table 4). On our basal diet, without any of the cholesterol-additives, our average plasma cholesterol for the rats is 84 mg %. When we fed the basal diet with thiouracil and butter added but no cholesterol or sodium cholate, it averages 158. With sodium cholate and the cholesterol but no thiouracil it rose to 540 mg for an average. If we fed the whole diet for one month (with sodium cholate, cholesterol, thiouracil and with 40% butter), the serum cholesterols went up to nearly 2000 and after 3 months, up to 3000 mg %.

When we vary the lipids in this diet (table 5)—very high levels of cholesterol developed with butter and with Crisco not so high. When we added three times the normal amount of salt mix, the cholesterol level rose still higher. With corn oil (compared with butter), cholesterols were much lower. Omitting thiouracil but retaining the butter, the cholesterol and the bile salts, and adding sodium cholate at three times the basal level, the cholesterol went up very high. We feel now that the sodium cholate is much more important than we originally realized. We have run a series where we dropped the sodium cholate to half and another series where we left it out entirely and the myocardial infarcts did not appear.

Here is a summary of results up to the summer of 1958 (table 6). Among 178 rats fed cholesterol, thiouracil, butter and sodium cholate in the diet, 25% in this large series, 45/178 developed infarcts. In individual instances, groups have gone up as high as 60%. Amongst another 175 fed variations of that diet where we changed the type of fat or changed the level of thiouracil, infarcts still developed but in varying percentage and generally lower.

The theoretical basis that we have used in these experiments is summarized in figure 31; with the atherogenic hypercholesteremic substances we produced local deposits of cholesterol and lipids with some local vascular damage; by adding the high amount of saturated fat we interfere with the protective fibrinolytic system (and/or increased coagulability) of the animals. These procedures together produced occlusive arterial thromboses, myocardial and other infarcts. This was our rationale for planning our experiments. The fact that we were successful does not prove the basis of our experiments, of course, but we are continuing on this basis for our further investigations.

In addition to the support provided by the Nutrition Foundation, portions of the experiments reported here were aided by USPH Grants Nos. H-1820, H-1968 and H-3060.

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Atherosclerosis—A Commentary

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ATHEROSCLEROSIS, particularly of the coronary and cerebral vessels, has received a most remarkable amount of attention in the past ten years. The more remarkable is that it was so long in coming, because surely it has been evident ever since the advent of mortality statistics that atherosclerosis was mankind's major killer through heart attacks and strokes. Our ignorance came to a head dramatically in President Eisenhower's heart attack and Stalin's death from stroke.

But several years before some satisfying groundwork was being laid for sound investigative approaches to the problem. Now, a decade later, research of a high degree of competence is under way. Only a few answers are in and these are not likely to satisfy the impatient. But we must take great care that the desire to give answers under the pressure of need does not overcome scientific prudence. There is some evidence, I am sorry to report, that this occasionally has been true.

The stimulation and fun of growing with a problem is one of the great rewards of research and here is a problem of major importance making its debut. Workers with every sort of investigative approach will be needed to solve the problem, for it is already apparent that it has many facets. Each must find its place in the whole.

I confess that I had planned on another speaker giving you a systematic presentation of the many and varied aspects. My presentation is, accordingly, just what it says in the title, a commentary and often a very casual one at that. But I hope you will gather from it impressions which are current with many of us in the field. These are some of the problems which worry us for which we may have answers but by no means correct ones. In short, I shall talk to you rather than lecture.

So let's begin with the fact that the male is a very inferior creature. It has been said this is a man's world, but I have pointed out on many occasions that it is in his wife's name. Maleness alone seems to be enough to give us a four to one edge on females in the matter of having a heart attack. Even though female sex hormones are on the drugstore shelf, it still remains a fact that most males are not willing to lick them by joining them.

But maleness is only an example of a facet of this multi-faceted problem. Among others are the question of its dietary origin, of the primacy of fibrin deposition and its overgrowth by endothelium, of its origin from the chemical changes inherent within the vessel walls themselves. There are so many facets it leads one to suspect that tenure is almost built into the investigator's job of finding the cause and cure of atherosclerosis.

Now can we, with such a great variety of approaches, agree on anything? Perhaps the following: atheromatosis is civilized man's greatest killer. Knowledge of its nature is primitive. It can be reproduced with uncertain fidelity in most animals. Women are less subject to it than men. Hyperlipemia and hypertension, aging, heredity, anatomy of the arteries predispose. Countries on high caloric, high lipid diets have a high incidence. No method of ante-mortem diagnosis is available. This is a sort of 'against sin' type of information but at least provides something relatively dependable with which to start.

The composition of plasma, the arterial pressure and rate of filtration of plasma constituents through the vessel walls probably are important. The cellular responsiveness of intimal tissues to filtered products from the plasma, normal or abnormal, is still another facet which has been much neglected.

This all suggests one of the general trends that is being established in the investigative field, namely the notion that it is hyperlipemia that in some way initiates atherosclerosis and that the hyperlipemia is due, at

least in part, to diet. A second trend is the notion of Duguid, and many other investigators in England, that atherosclerosis is initiated by laying down of fibrin, the overgrowth of the fibrin by endothelial cells and then possibly the secondary deposition of lipid in this cellular cushion.

Many people simply don't believe this but Dr. Astrup has some evidence, along with others, that the plasmin system is the one which dissolves fibrin and that there is an equilibrium between the deposition and resolution of the fibrin. Deposition and resolution may be occurring constantly. And it is not too much to suppose that deposition might overtake resolution leaving residual fibrin stuck to the vascular endothelium. This is a very attractive hypothesis, however, some of the so-called 'coagulationists' want no part of this theory. They find no substantial evidence to prove it—and there we are!

Now, unfortunately, this can be said of almost everything that I, or anybody else, can say in the field. For instance, some say that fat increases coagulation; others say it does not. Some think too much fat in the diet causes atherosclerosis; others think carbohydrate is the offender.

The lipid infiltration theory is not a very good theory, but it is one that I think helps visualize why some people think that lipids have much to do with the development of atherosclerosis. I will not try to develop it for you today, and if you are interested I have discussed it at length in a Conner lecture (1). Put very simply it states that plasma lipids constantly pass through the blood vessel wall into the extracellular space, pass into the lymph and that which is not metabolized poured back into the blood stream. There is always the possibility that some gets stuck, breakdown occurs and insoluble fats are deposited within the vessel wall.

Most people would grant the possibility that the breakdown products, for instance of the lipoproteins, may act as foreign bodies if they lodge in the blood vessel wall. Dr. Florence Sabin a number of years ago showed the body reacted vigorously to free fatty acids when they were injected into tissue. Fatty acids are fibrogenic and this is a possible way the scars could be formed, which characterize atherosclerosis.

You are all aware that the lipids in the blood are carried as lipoproteins, and this probably is the body's answer to a rather complicated problem. The only insoluble substances I can think of that the body faces are lipids. Therefore a way of solubilizing them had to be found. Protein was added and the resultant lipoprotein is water miscible.

These big lipoproteins—and the beta lipoprotein is the biggest one of them and the most heavily laden with fat—have the potentiality of breaking down within the vessel wall, and therefore, the possibility of liberation of free fatty acids and the formation of scars. This then is just a way of visualizing one mechanism of atherogenesis.

Since this is a conference of nutrition, I shall briefly discuss a few highly selected topics possibly related to atherosclerosis. I think you are familiar with Ancel Keys' well-known chart in which there is shown the relationship between deaths per 1000 and the fat calories consumed. It rightly suggests that there is a direct relationship between fat content of the diet and the amount of heart disease—a bad thing for us who like to eat, if true.

But there is another side to this. John Yudkins' graphs (2) show the danger of the associative type of thinking in science. Cause and effect often get confused with what is only an association. For example, Yudkins' mortality figures for heart disease show the relationship with animal fat intake is not very good.

His next illustration shows the relationship to vegetable fat is close. It might follow that if one eats too much vegetable fat one would get fatal heart disease. The next shows that the amount of money one makes is even more closely related to the amount of heart disease, and the last figure shows that the number of television licenses that are issued in England yields the closest fit. So you can conclude that if one buys a television license in England one probably will have a coronary heart attack. From some of the television programs I have seen, this is altogether possible.

The problem of the relationship of the fat content of the diet and mortality from heart disease is so important that I have tended to make fun of it just to emphasize that it is not yet settled one way or another.

Our convictions sometimes change so fast it makes one a little breathless keeping up

with them. The first dietary suggestion was the low cholesterol diet. Of all the stupid things anybody could do, this was it, because everyone knew that cholesterol is synthesized by the body. If cholesterol is withdrawn from the diet, the body synthesizes enough cholesterol to make up the deficit. The body, as usual, is smarter than the person who inhabits it.

I tried the low-cholesterol diet and lost weight as well as friends, and then woke up to the fact about 9 months later that I was getting nowhere. This, I fear, is about a normal intellectual gestation for me.

This diet was followed by the strict low-fat one which in some people certainly could lower blood cholesterol. But it was too strict and most people felt they would prefer sin to going on with it.

Next there was the very important contribution of Dr. Ahrens, Dr. Beveridge and Dr. Kinsell, which I think now is well accepted. They showed that there is a relationship between the blood lipids and the degree of unsaturation of the dietary fat. It is a complicated and an interesting picture, and I am sure there is even more to it.

Probably we can say with justification that diet has something to do with atherogenesis, but if they press you and say, "Now, what are you going to do about it, leave those pats of butter on your plate because you might get fat". If you don't get atherosclerosis at the same time, that might be too bad for your wife if she is in a hurry to inherit the world.

So the problem is, "Can we substitute something for the high fat content of our diets?" We were interested in this with Dr. Helen Brown at the Clinic because we feel that something cannot be taken away from the American public without giving it something in return which it likes as well. If there ever was an example of this it is the cigarette business. Some tried to scare people into quitting smoking. Day before yesterday in the paper it was stated that only 6% of people quit smoking because they were scared of lung cancer. The other side of the coin is that the American public in the face of the scare increased its cigarette smoking 6%.

Now, I think we should remember this important lesson. Go into a good restaurant, watch a waiter prepare your baked potato and see him drop four pats of butter into it. This will make you realize that Americans are not going to pay the slightest attention to what we as scientists have to say. It seems to me our problem is not to tell them what they can't do but rather to tell them what they can do and give them something to do it with.

The problem we set ourselves was whether a 'way of life' could be found rather than a diet which would provide fat calories which assisted in reducing plasma cholesterol rather than raising it. The term diet was avoided because the public will not eat a 'diet' over any long period of time.

Dr. Brown has proved herself a very expert cook and has prepared recipes of many articles of food which are just as good, and often better, than the usual. Unsaturated oils have been substituted for the saturated wherever possible, such as shortening, margarine, salad oil, etc. It turns out that this is a perfectly practical way to live. We have adopted it in our home for the past year and a half. The trick is to avoid telling the family that there is anything unusual happening. Just as soon as an 'experiment' or a 'diet' is mentioned, children won't like the food, no matter how delectable it is. A sure way to cause trouble is to say, "Now we are trying an unsaturated oil in your biscuits instead of shortening."

People do change their tastes in food. Anyone, for instance, who can learn to drink gin, ought to be able to use an unsaturated oil, or get along with less fat in the food.

Now we have ample evidence that this 'way of life' is associated with considerable and consistent fall in plasma cholesterol of normal people. Examples of this evidence have recently been published (3).

Of course, we have not solved the problem. I think the food patterns Dr. Brown has now made up are in many ways very acceptable. That is, parts of them are very acceptable. Others are not good at all. They must not only all be good, but they must be salable. For unless this kind of food can be made commercially available, it will have little more than laboratory interest. So far the food industry, with one notable exception, has shown no interest in this kind of investigation.

What can be practically recommended as a way of life which might help in reducing the dreadful toll of heart attacks? I have written

down some recommendations that appear safe and sane to me, but I am fearful that we scientists are making so many claims in public that it is likely to say, 'A plague on the whole thing.' People cannot be expected to live in fear of death, but rather they must live as though they were going to live forever.

There is one other thing we should be careful about and that is we are gradually being jockeyed into the position of prohibiting everything. We had better stop telling the public what it can't do and tell it what it can do. In the last few years we have told them they shouldn't eat fat, they must avoid stress, they should not lead sedentary lives and they should not smoke, drink so much alcohol or eat so much food. The public hardly knows what to believe because, as somebody said, if you drink, drive, do not park because accidents cause people.

Let's keep our notions to ourselves for a while until we know whether they are going to prevent atherosclerosis, or at least do good in one way or another. It is all good clean fun among us, but when we begin to peddle some of our ideas to the public, the trouble begins.

I think it fair to suggest reducing weight, if you are obese. As Fred Stare has put it, by eating less you live longer to eat considerably more.

If your heredity is bad as regards heart disease, and your cholesterol and/or lipids are too high, it is probably fairly smart to reduce them. I say this with certain reservations, because while I believe the evidence is convincing that if one has a persistent hyperlipemia of sufficient degree long enough, coronary disease will develop. But in the area of 250 mg/100 ml of blood cholesterol, the importance of blood cholesterol level may be greatly reduced. We are not sure whether the average level in Americans is already at too high a level compared with other nations where heart attacks are much less common. Some say we should try to emulate the Bantu but I would still rather be Irvine Page than a Bantu, though some of you may think this debatable.

It would probably be wise to reduce the fat content of our diet if for no other reason than to avoid getting fat, and then consider whether to change the quality of it from the less to the more unsaturated. Hypertension probably has some sort of relationship to the problem, at least as shown by the Framingham observations and, therefore, maintenance of strictly normal arterial pressure is important.

In general, we should avoid excesses of all sorts—but just don't miss anything.

It might be wise to increase the amount of exercise, if only to quit being so lazy. In this connection, Dr. Lewis and I have some interesting results on rats consuming Dr. Hartroft's diet. One group sat on their derrieres and did just about what most people do, while the other group were in cages that periodically revolved. Even under the latter circumstance a few of the rats just rolled with the cage—a not uncommon human practice. But those which exercised had lower blood cholesterol than their sedentary associates. It is possible that exercise could aid in preventing atherosclerosis by reducing blood lipids as well as its massaging action on the walls of the blood vessels. If it seems good for rats it probably would be good for certain people. Whatever the mechanism, I like exercise and, therefore, everyone should take it.

Figure 1 proves that Dr. White is not the only person who believes in exercise and takes it. This, believe it or not, was taken in San Angelo, Texas, and we were starting out to the auditorium to give speeches. Dr. White is one of the most remarkable people in the

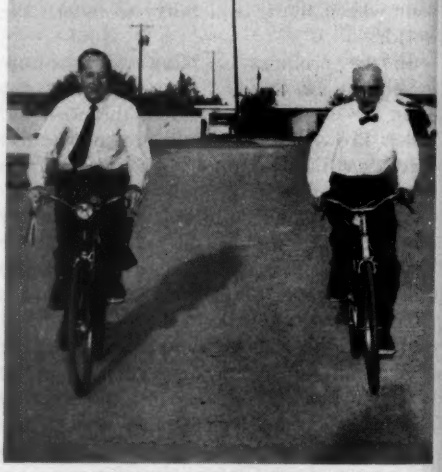

FIG. 1.

world in the sense of his complete belief in these things. He not only says them but he does them, and he makes everybody else do them, as you can see here.

One last bit of information: I think everyone recognizes there are differences in species, but there are differences among people as well. I have a graph of my cholesterol and lipoprotein which has been determined over a period of years. On a low-cholesterol, low-fat diet, I went from a hypercholesterolemic coronary type to really very low cholesterol levels for me, and then my lipids came back up after my wife and I got sick of the whole business.

I also found that every time I would go away on vacation my cholesterol dropped to a lower point and then came back up when I returned to Cleveland, and then it dropped again the next vacation.

Another graph shows Dr. Lena Lewis' blood lipids, and every time she goes on vacation hers go up. The answer here is obvious: let her stay at home and do the work, and I will go away on vacation and everybody will be happy and avoid heart attacks.

I realize I have not presented you with a well-organized and inclusive discussion of the many facets of this multi-faceted problem. If I can convince you only that the lines of research should be kept wide open, that everybody in this field has his place, that all these bits of evidence are beginning to form a discernible pattern, and that we must not allow ourselves to get in a position where we are being pressured into giving answers before we have the answers, I will have fulfilled my role. This is a very young and very immature field. The men in it are of high competence. It now has its own society, the American Society for the Study of Arteriosclerosis, and so it has come of age.

I would simply end by giving you a bit of my baseball cousin's philosophy—you know Satchel Paige, the pitcher. He sums up a philosophy which I wish all the Pages would follow. He says, "Avoid fried foods which angry up the blood. If your stomach disputes you, lie down and pacify it with cool thoughts. Keep the juices flowing by jangling around gently as you move. Go very light on the vices, such as carrying on in society. A social ramble ain't restful. Don't look back; something may be gaining on you."

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Comparative Studies on the Effect of Dietary Fats on Serum Cholesterol Levels

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AS DR. PAGE has pointed out, one of the few things we can agree on is that fats do something to serum cholesterol. I think this has been a uniform experience by everyone in the field. The real question is what the different fats or amounts of fats do.

From the literature reports concerning the influence of dietary fats upon the serum cholesterol levels in man, one finds that: *a*) The cholesterol lowering ability is related in a definite way to the ratio and amount of the saturated and polyunsaturated fatty acids in the fat, the saturated acids raising the serum level and being twice as active per gram as the polyunsaturated acids are in lowering the serum level, and the monounsaturated acids having practically no effect (1); *b*) that the lowering of the serum level is related to the total degree of unsaturation (iodine number), presumably with both the mono- and polyunsaturated acids being active in proportion to their degree of unsaturation (2); *c*) that the polyunsaturated acid, linoleic acid, is the primary factor which lowers the serum cholesterol level (3); *d*) that the addition of a saturated oil to a highly unsaturated oil, thus lowering the proportion of polyunsaturated acids and raising the saturated acid content, does not necessarily elevate the serum cholesterol level produced by the unsaturated oil (4); *e*) that hydrogenation of corn oil which markedly lowers the amount of linoleic acid (polyunsaturated acid) in it, has little influence upon its ability to lower the serum cholesterol level (5); and *f*) that corn oil (and possibly other oils) have specific abilities to lower the serum cholesterol unrelated to their fatty acid content (1, 5). It is apparent that some of these findings are contradictory. Since one cannot conclude *a priori* that any of the above reports are wrong, it is perhaps more likely, and certainly more generous, to suspect that the variable conditions under which the above studies were done account for the variability obtained and the apparent discrepancies. Each finding may be true under the conditions of the experiment. The difficulties of complete control of the diet and other genetic and environmental factors are always a serious limitation in studies upon human beings. Such limitations, as well as the time and cost involved, provide the primary impetus to search for experimental animals which may serve as an appropriate experimental model for the human being.

The rat fed cholesterol and cholic acid develops hypercholesterolemia and atherosclerosis. The influence of dietary fats upon the serum cholesterol and development of atherosclerosis under these conditions can rather easily be determined. From a study of some 50 different fats and mixtures of fats we find (6) that the saturated fatty acids and linoleic acid (the principal polyunsaturated acid) act synergistically in lowering the serum cholesterol level (fig. 1). The product obtained by multiplying the saturated acid by the linoleic acid has a high negative correlation with the serum cholesterol level. Olive oil, which contains very little of either of these kinds of fatty acids but which contains much oleic acid (monounsaturated fatty acid), gives very high serum cholesterol levels.

Dr. Portman has limited data upon the effect of different fats in the cholesterol fed monkey. The addition of hydrogenated oil and coconut oil to corn oil appears not to raise the serum cholesterol level. Olive oil and an impure triolein preparation resulted in somewhat higher serum cholesterol levels than did the more saturated oils fed. Thus, the indication is that this species may respond in a manner similar to the rat.

In hypercholesterolemic human subjects

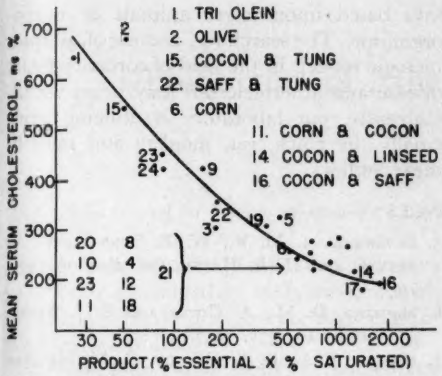

FIG. 1. Apparent synergistic action of saturated fatty acids and linoleic acid (essential fatty acid) in lowering serum cholesterol in rats fed a cholesterol-cholic acid containing diet.

TABLE 1. EFFECT OF SAFFLOWER OIL VERSUS AN EQUAL MIXTURE OF SAFFLOWER AND COCONUT OIL UPON THE SERUM CHOLESTEROL VALUES OF HYPERCHOLESTEROLEMIC PATIENTS

	Control	Safflower	Mixture
Group A.....	345	250	241
	Control	Mixture	Safflower
Group B.....	379	272	287

(7) fed a formula diet containing 40% of the calories as fat, the inclusion of safflower oil, which is very high in linoleic acid, causes a pronounced fall in the serum cholesterol level (table 1). The substitution of half of the safflower oil with coconut oil (practically all saturated fatty acid), thus decreasing the linoleic acid content by about one-half and raising the saturated fatty acid proportionately, was equally effective or slightly superior in lowering the cholesterol level. Thus, insofar as this study goes and in this respect, the rat, the monkey and the man responded similarly.

On the other hand, olive oil was markedly hypercholesterolemic in the rat but produced some fall in the serum cholesterol level in man. Apparently, the rat did not provide a completely adequate model for man.

We have recently begun studies on the chick. This is a convenient animal which develops atherosclerosis under ordinary conditions. Studies were done in which some 50 different fats were fed to groups of chicks which also received small amounts of cholesterol. In these studies the kind of fat was again found to exert a marked influence upon the serum cholesterol level (fig. 2). The findings to date indicate that no synergism between the saturated and polyunsaturated acids occurs; rather, the ability of a fat to lower the serum cholesterol level under these conditions, and in this species appears to be primarily related to the iodine number, i.e. the total degree of unsaturation. Saturated fats, such as coconut oil, produced high serum levels and these fell proportionately as more unsaturated fatty acids were included in the diet. The highly unsaturated vegetable oils, such as safflower oil and corn oil, produced the lowest serum levels. There is also evidence that corn and cottonseed oil have some action in lowering the serum cholesterol level in addition to their unsaturated fatty acid content.

The chick, rat and monkey respond to dietary fat in ways, similar and different, to those observed in man. From our preliminary studies, the chick may appear to be the most appropriate model, although this may be premature and based upon too little data

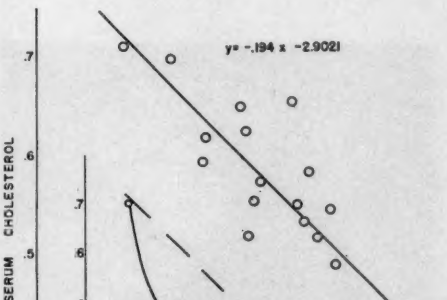

FIG. 2. Relationship between the iodine number of a series of oils and mixtures of oils and the serum cholesterol values in cholesterol fed chicks. Insert (lower *left*) indicates values obtained with mixtures of coconut oil with corn oil or cottonseed oil. These do not appear to follow the relationship found with most of the oils.

upon man as well as upon animals. The job of course, is to find out why and how the fats do what they do. The history of nutrition has shown that the isolation, identification and the determination of the function of each of the vitamins and the other essential nutrients required the use of appropriate biologic assays based upon lower animals or microorganisms. The search for, and use of, simpler biologic models in the field of coronary heart disease and atherosclerosis may be as useful. Currently, our laboratory is utilizing principally the chick, rat, monkey and man in these studies.

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Production of Atherosclerosis in the Rat

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FIRST, LET ME MENTION that these experiments have been conducted in collaboration with Dr. Bernard C. Wexler, Research Associate of the May Institute.

We have found in the white rat that females which have been bred frequently and given ⅓U ACTH three times a week for 7 weeks develop a really explosive kind of arteriosclerosis. These animals are approximately one year old. They are fed ordinary laboratory chow without added fat or salt. If the animals are previously unilaterally nephrectomized, the atherosclerosis is greatly intensified. The lesions involve not only the aorta and the peripheral vessels but are frequent in the coronary arteries. Typical coronary sclerosis and infarctions are observed with rather striking resemblances to the human disease.

The serum cholesterol does not change in the early weeks during the development of the atherosclerosis. Figure 1 shows you the full-blown pathology. The heart and the aorta from the experimental animal is shown on the left and contrasted with a control of the same age on the right. The experimental animal has a marked widening of the aorta, enlargement of the heart and extensive arteriosclerotic changes throughout the aorta.

In figure 2 there is portrayed an arteriosclerotic aorta that has ruptured and produced an aneurysmal dilatation. The point of separation of the elastic tissues in the aorta can be seen in figure 3 which gives a higher-powered view of the same aneurysm as shown in figure 2.

The next figures, 4, 5, and 6, present the marked sclerosis in the coronary arteries with almost complete obliteration of the lumen. Only occasionally as shown in figure 6 have we observed foam cell accumulation.

A thrombotic type of lesion appears in figure 7. The atherosclerotic changes in the vessel wall can be plainly seen. The thrombus is being rechanneled in two places. This section is taken from the abdominal aorta.

Finally, let me show a very early type of lesion which involves both the intima and media of the artery. Compare figure 8, which

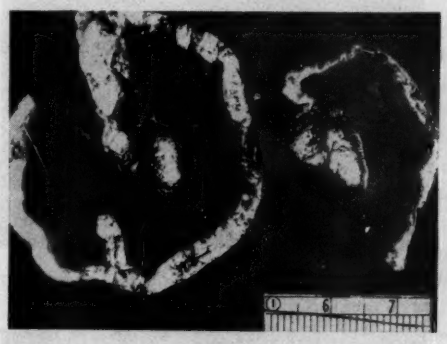

FIG. 1

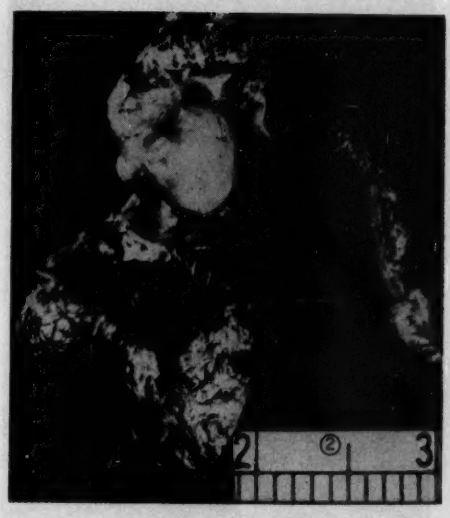

FIG. 2

FIG. 3

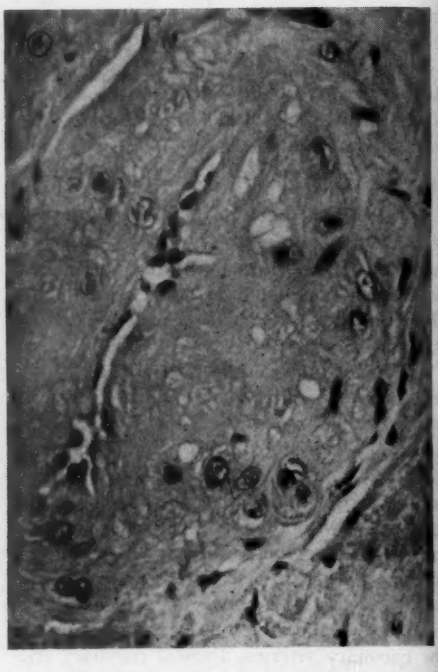

FIG. 4

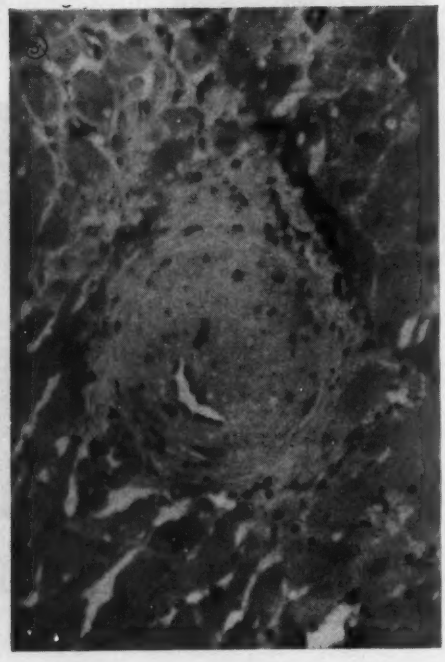

FIG. 5

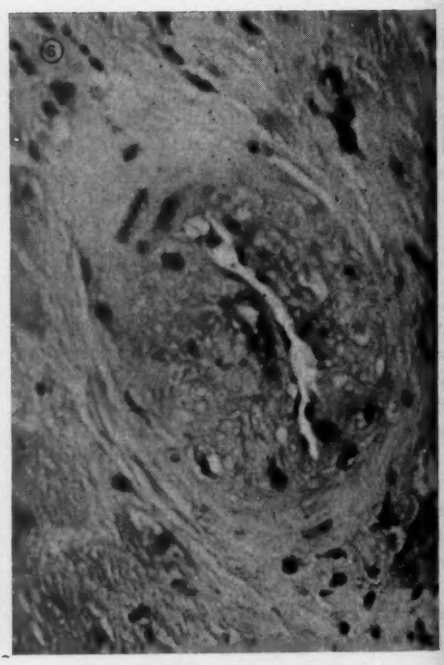

FIG. 6

FIG. 7

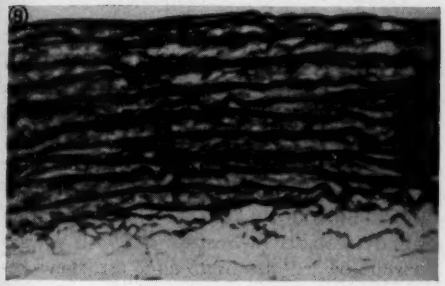

FIG. 8

gives the normal arrangement of elastic fibers in the rat aorta, with figure 9. Notice the swelling and distension of the elastic fibers. Of special interest is the intimal plaque

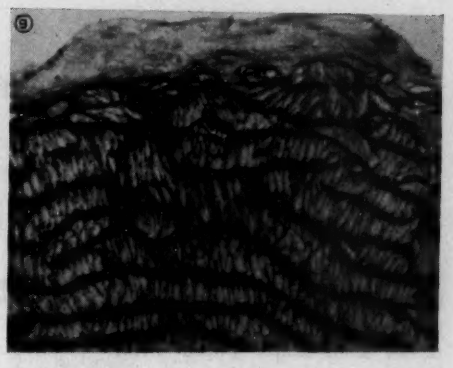

FIG. 9

composed of fibrinous material and containing no fat. We hope that these early lesions can be used for actual chemical study of the pathogenesis of this type of arteriosclerosis, and at present we are conducting a search for mucopolysaccharides (in collaboration with Dr. G. Kittinger).

Because so many nutritionists are present in the audience, I would like to mention that it has been hitherto extremely difficult to produce typical atherosclerosis in the rat, an animal which makes an ideal tool for study of the nutritional and metabolic aspects of this disease, as well as being such an easy animal to handle in the laboratory.

Obesity as a Nutritional Disorder

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University of Pittsburgh

OBESITY, or excessive fatness, is the commonest form of malnutrition in the well-nourished peoples of the world. It has received recognition as a major public health problem because of the association with it of many serious chronic degenerative diseases, one of which, atherosclerosis, is a leading cause of death in the United States and in many other technically-developed and well-fed countries. Obesity has long been regarded as a troublesome, as well as ominous, medical problem by physicians because of the great difficulty they have had in treating it. Contrariwise, and I think somewhat unfortunately, physiologists and nutritionists, who have not had direct contact with the clinical problem, have regarded obesity as quite a simple disorder, i.e. 'simply a matter of overeating.'

Today I should like to discuss certain aspects of this unsolved problem from the points of view of *a*) the definition of obesity, *b*) its prevalence, *c*) its multiple causes, *d*) its liabilities in terms of the concomitant diseases that afflict middle-aged persons who are overweight and *e*) the response of obese persons to diet therapy as measured by weight loss, changes in symptomatology and alteration in clinical and biochemical signs of illness or disordered function.

The clinical material to be presented is drawn largely from our own study of obesity in men and women of middle age, 40–59 years of age, at the University of Pittsburgh Medical Center. The work has been carried out by a team of individuals including physicians, nurses, nutritionists, dietitians, medical technologists and biochemists. In addition to our regular staff, we were fortunate in having the assistance of a large number of volunteer dietitians who were recruited by the Nutrition Council of Allegheny County and the Pittsburgh Dietetic Association. This study has led us to adopt the view that obesity, like many other chronic illnesses, is a psychosomatic disease for which there are both psychological and somatic determinants.

DEFINITION

The clinical definition of obesity must necessarily be arbitrary. Since depot fat is a physiological constituent, the problem centers around the question of how much body fat is too much. In young adults in the third decade, about 12% of the body weight of the male and about 19% of the body weight of the female is depot fat (1). The distribution of body weights in healthy adults is always skewed toward the high side, the skew becoming more prominent in older populations as the prevalence of obesity rises. A normal distribution is approached, although not reached in young adults 20–29 years of age. If one inspects the distribution curves for both males and females in this age group below the median values, one finds that 47.5% of this half, i.e. the population encompassed by two standard deviations below the median varies in weight from 12 to 18% below the median value (2, 3). If, then, one assumes that a similar distribution on the high side of the median would exclude the obese individuals present in this young population, one could conclude that an increase in weight of 15% above 'desired weight,' i.e. median weight at age 25, would occur by chance only 1/20 times in a 'normal' population, and might be considered the line of demarcation between the non-obese and the obese. This also assumes that differences of build, bone size and muscularity would be randomized in large populations which is probably not entirely true. In appraising an individual, specific corrections could be applied for these parameters. In 'standard' individuals in the third decade, a 15% in-

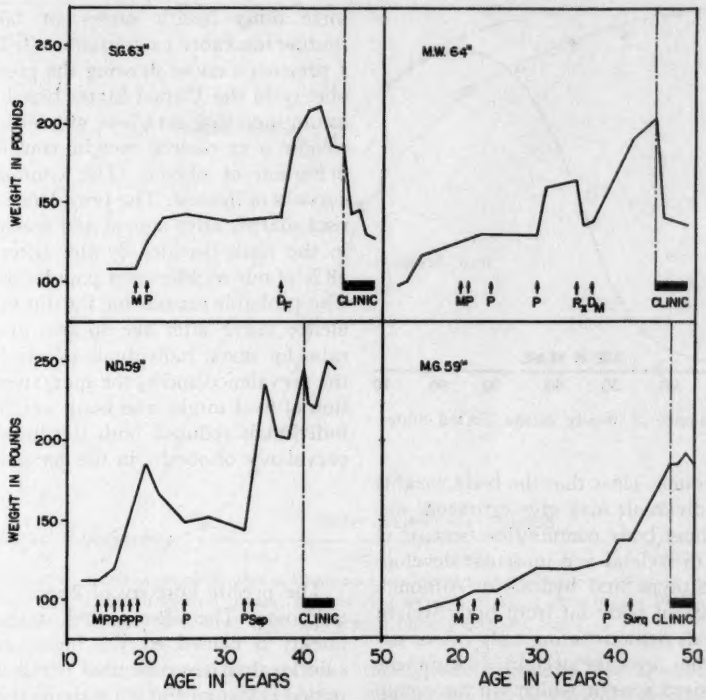

FIG. 1. Life weight curves of obese women in relation to social and medical events. Abbreviations used: M = marriage; P = pregnancy; Sep = separation from spouse; D_F = death of father; D_M = death of mother; Surg = surgical intervention. Broken line indicates entry to the Nutrition Clinic and black bar denotes time of follow-up in the Clinic.

crease in body weight would correspond to an increase in body fat from 12 to 22% in males, and from 19 to 29% in females. If one accepts the 5% probability level as significant, these increases in body weight and body fat might be considered to be the statistical line defining obesity in the average man or woman.

Another novel approach to the definition of obesity in man has been made by Behnke (4). In guinea pigs, approximately 4% of the lean body weight of males and 7% of the lean body weight of females is fat-free adipose tissue (5). This normal complement of fat-free adipose tissue has a maximum capacity for lipid storage which approximates 20% of body weight in the male and 28% in the female. If lipid is stored in these animals beyond these limits in response to long-sustained positive caloric balance, new fat cells are formed to accommodate this fat and the fat-free 'adipose tissue' increases. Apparently, macrophages and other elements of the reticulo-endothelial system assume the role of adipose tissue cells under these conditions. When this alteration in storage mechanism occurs, representing essentially a pathological change, Behnke suggests that obesity may be said to exist. It is of interest that when these data are applied to man (4), the lines of demarcation between the obese and non-obese (20% fat in the male and 28% fat in the female) correspond to increases in body weight of 13% in males and 14% in females beyond 'desired weight', which is in agreement with the statistical definition propounded above. It appears, therefore, that both statistical and physiological arguments can be advanced to suggest that when the body fat content of an individual of average body composition rises to the point where body weight increases 15% above the median weight of healthy individuals age 25, of the same height, he should be considered obese.

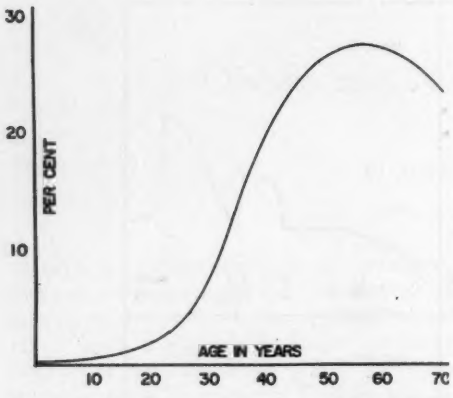

FIG. 2. Prevalence of obesity in the United States.

It is, of course, clear that the body weights of given individuals may give erroneous impressions about body composition because of differences in skeletal and muscular development, somatotype and hydration. Although the appraisal of body fat from body weight in individuals demonstrating only minor departures from average weight (within the 15% of desired weight which we have considered normal) requires more sophisticated methodology than the scale, the diagnosis and rough appraisal of body fat content of the truly obese individual can be accomplished with simple methods. Four methods which are useful in appraising body fat content might be mentioned. These are *1*) the visual method (the look); *2*) the gravimetric method (the scale); *3*) the digital method (skin-fold pinch); and *4*) the aquatic method (body density and body water estimations). In the clinical diagnosis and treatment of obesity, information obtained by the first two is usually sufficient. Although it is unusual to have to depend upon more than the first three for clinical appraisal, the fourth method is useful in research.

PREVALENCE

Data on the prevalence of obesity are sketchy and incomplete, mainly because very few of the studies available have been designed to determine the prevalence of this condition. Generally, height and weight measurements were carried out secondary to some other health survey or taken from routine insurance examinations (6–8). Figure 1 presents a curve showing the prevalence of obesity in the United States based upon the assumption that a 15% or greater increase in weight over desired weight constituted the definition of obesity. The contour of this curve is of interest. The prevalence of obesity rises sharply after age 30 and reaches a peak in the sixth decade. By the criterion used, 28% of our middle-aged population is obese. The probable reasons for the dip in the prevalence curve after age 60 are: *a*) mortality rates for obese individuals selectively reduce the prevalence and *b*) the spontaneous reduction of food intake and body weight in older individuals reduced both the incidence and prevalence of obesity in the geriatric group.

ETIOLOGY

The precise etiology of obesity in man is unknown. The oft-repeated statement that obesity is caused by the ingestion of more calories than are expended in the same time period is factual but is a statement of the conditions which are required for depot lipid deposition rather than a statement of the cause of obesity. This is analogous to saying that the cause of edema is a positive salt and water balance, or that the cause of alcoholism is the excessive ingestion of alcohol. In all three situations, the true causes—and they are undoubtedly multiple—are to be found in the factors causing a disturbance in homeostasis within the organism. In the case of obesity, the problem relates to factors which cause an inappropriately positive caloric balance and eventually an inappropriately high body lipid content. In times of growth, convalescence, pregnancy and lactation, a positive caloric balance is physiologic and essential. In well-nourished adults, a positive caloric balance is unnecessary and undesirable.

The taking of food is, of course, a basic urge which arises within the central nervous system and is required for self-preservation. The homeostatic mechanisms which adjust the intake of food appropriately to the expenditure of energy are not known with certainty and probably involve both neurologic and biochemical pathways and signals. Glucostatic, lipostatic (9) and thermostatic

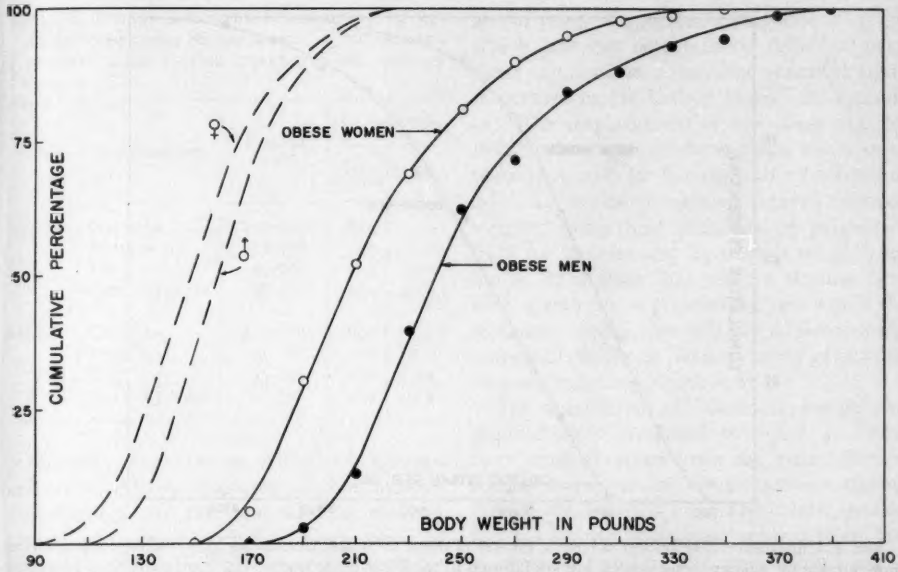

FIG. 3. Cumulative distribution of weights of obese and non-obese men and women 40–59 yr. of age. Open circles represent weights of obese women and solid circles, weights of obese men in the Pittsburgh Study. Dotted lines represent weights of 'control' male and female populations (see text).

mechanisms (10) have been suggested but none as of this date has been adequately validated in man.

The hypothalamus appears to be the coordinating center for both afferent and efferent impulses which traverse the basic reflex arc adjusting food intake to tissue needs. This reflex may be looked upon as a servo mechanism although the signals which account for both the short and long range control of appetite in relation to exertion and changes in body composition are still unknown. The cerebral cortex undoubtedly exerts an important influence upon this reflex in man. Neural pathways exist from the frontal lobes and other parts of the cortex to the hypothalamus and provide the anatomic basis for the well-established relationship between the psyche and appetite. Certainly psychogenic factors are of great importance in the onset of human obesity. In our own studies (fig. 2) we have found that such meaningful and often traumatic experiences such as marriage, pregnancy, surgery, menopause, death or separation of a loved one may herald the onset of obesity. Under these conditions 'conflicts' arising in the frontal lobes could generate signals which might modify the activity of the satiety center in the ventralmedial nucleus of the hypothalamus and lead to relative hyperphagia. Further research is needed to clarify the homeostatic mechanism which operates in the healthy individual so that a more rational basis will become available for pinpointing defects which occur in disease.

Mayer (11) has been able to distinguish between two types of obesity in experimental animals. The first he calls 'regulatory' and pertains to those disorders in which the reflex arc or its components are disturbed (hypothalamic extirpation, gold-thioglucose treatment); the second he terms 'metabolic' and pertains to those disorders in which erroneous signals are generated because of a primary metabolic defect leading to excessive fat synthesis. The extent to which this classification can be applied to man is not apparent at this time.

Finally, it should be pointed out that the widely-accepted clinical classification of obesity (12) as being either exogenous or endogenous is meaningless. No obesity of any etiology could develop in the absence of a positive caloric balance. Conversely, no obesity would occur if the homeostatic mechanisms adjusting food intake to energy expenditure were operating correctly. All obesity, hence, is both exogenous and endog-

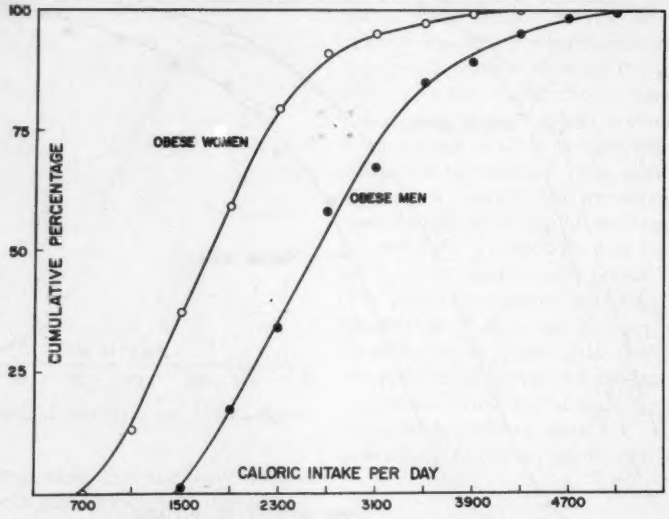

FIG. 4. Cumulative distribution of caloric intakes of obese men and women 40–59 yr. of age. Open circles show intakes for women; solid circles, intakes for men in the Pittsburgh Study.

enous. Stating this truism, however, does not solve the problem of its causes. The answer to the problem of the etiology of human obesity can come only from a protracted study of the status of the homeostatic mechanisms which govern food intake in normal and overweight humans. The avidity with which obese persons conserve nitrogen (13) and the difficulty with which they generate ketone bodies (14) may be 'somatic traits' which bear on the control of energy exchange.

LIABILITIES

It is now well recognized that certain chronic diseases, which are serious causes of morbidity and mortality in man, such as coronary artery disease, hypertension, diabetes and gall bladder disease are associated to a significant degree with obesity (15). Further, the insurance companies have established that the death rates of obese individuals from these same diseases are increased above those of normal weights. In those 25% or more over average weight, the death rate is about 1.7 times normal, and at 40% overweight it increases to 2.2 times the normal rate. Diabetes and cardiovascular renal diseases contribute greatly to this increased mortality rate. In all overweights, the likelihood of developing diabetes is about three times that of normal weights and, if those 25% or more overweight are considered, the rate is approximately 8 times normal.

The meaning of this association is still not entirely clear. It would be remarkable to me if obesity could influence the development of pathological changes in three separate systems, namely, the vascular system, the endocrine system and the digestive system by some simple direct mechanism. The views on this association vary widely from the view that explains this association as the basis of cause and effect to that which represents it as completely fortuitous. It is probable that the truth lies somewhere between these two extremes. To study further the nature of this association, we undertook a study of obesity at the University of Pittsburgh some 4 years ago.

The approach we used was to characterize clinically and metabolically a group of obese individuals 40–59 years of age, and then to measure the effect of diet therapy aimed at weight reduction upon their health. Over the past 4 years we have assembled in our Nutrition Clinic a group of some 450 obese subjects of middle-age, at least 25% over desired weight, of whom 80% are women. The subjects were obtained by referrals from

TABLE 1. DAILY AD LIBITUM FOOD INTAKE OF 325 OBESE WOMEN AND 86 OBESE MEN AS DETERMINED BY 7-DAY FOOD RECORD CORRECTED FOR WEIGHT CHANGE

Group	Food Constituent	Range of Intake	Average Intake	
			Constituent	% Cal.
Women	Calories	700–4550	1815	
	Protein	28–158	74	16.3
	Fat	25–204	83	41.2
	Carbohydrate	58–405	193	42.5
Men	Calories	1410–5130	2690	
	Protein	41–188	110	16.4
	Fat	55–244	130	43.4
	Carbohydrate	60–508	270	40.2

practicing physicians in Allegheny County and reported to our clinic for a comprehensive examination. At the first visit a medical history and diet history (16) were taken, a physical examination given, and laboratory studies such as urinalysis, chest film, electrocardiogram and determinations of serum protein, blood sugar, hemoglobin, blood lipids and serum lipoproteins carried out.

These subjects were then given a food diary and asked to return in one week with the 7-day record of their dietary intake—presumably at their usual ad libitum rate—and the findings of this dietary record were then compared with the initial dietary history. Any positive physical findings of the previous week were reviewed and all the laboratory measurements repeated. This dual set of observations then became the base line against which the effect of diet therapy and weight reduction was measured.

Some of the characteristics of our study population are presented in the next five figures. Of 448 subjects for whom data are tabulated, 360 are women and 88 are men. The women averaged 49 years of age and the men 46. The mean height of the women (without shoes) was 63 inches whereas that of the men was 68 inches. A cumulative distribution plot of their weights is presented in figure 3. The median weight for the women was 205 pounds; for the men 235; the respective mean weights were 218 and 249 pounds. For comparison, the data from a 'control' population are described by the dotted lines. These latter curves represent the weight distributions of the inhabitants of Bergen, Norway, 40–59 years of age, studied by Boe *et al.* (7) which are not appreciably different from those obtained in a medical actuarial study of persons in the United States and Canada (2). The displacement of our obese population to the right at the median value is 57 pounds or 39% for females and 77 pounds or 49% for males. Reckoned against 'desired weights' (17), these shifts are 79 pounds or 63% for females and 84 pounds or 56% for males. It is clear that we are dealing here with a very obese population, one which the insurance companies tell us is particularly vulnerable to illness from a variety of chronic diseases and early death (18).

The distribution of caloric intakes for this population is presented in figure 4. These data were obtained from the 7-day dietary record corrected for weight change during the one-week period (19). The caloric intakes for our female population ranged from 700 to 4300 cal., and for the males from 1400 to 5100 cal. The median intake for females was about 1700 cal.; for males, 2600 cal. The former figure is in agreement with that obtained by Swanson *et al.* (8) in a study of 427 Iowa women 40–59 years of age. No differences in average food intake between obese and nonobese women were found in that study. These data show that although obese individuals consume a wide range of calories, the average obese person is euphagic and hence is expending less energy than the person of normal weight. If we assume that the euphagic range of calorie intake by sedentary women in this country is 1500–2100 cal., then 30% of obese women in our study are hypophagic and only 25% are the hyperphagic gluttons all obese individuals are suspected of being. The same percentile distribution of caloric intakes among hypophagics, euphagics (2300–2900 cal.) and the hyperphagics is noted in the males in our study.

A further breakdown of this dietary information among the major nutrients is shown in table 1. In both obese men and women, we find that approximately 16% of calories are derived from protein, 41–43% are derived from fat, and approximately 41% are derived from carbohydrate. Obese individuals eat a fairly typical 'American' diet in terms of distribution of fat, protein and carbohydrate, as also noted by Beaudoin and Mayer (20). The supposed preference of obese persons for

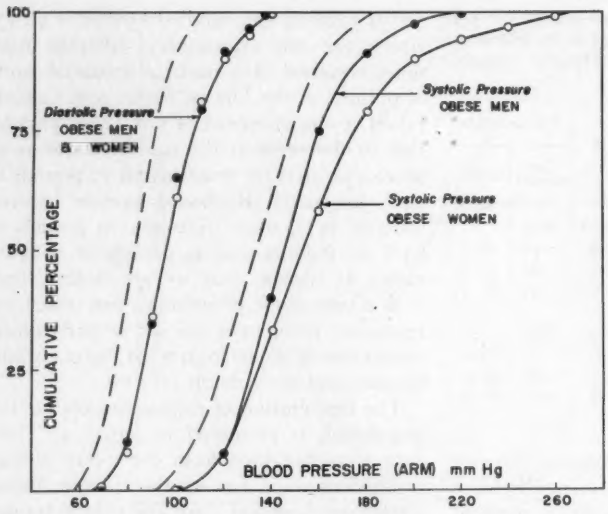

FIG. 5. Cumulative distribution of blood pressures in obese and non-obese men and women 40–59 yr. of age. Open circles represent pressures (systolic and diastolic) for obese women and solid circles represent pressures for obese men in the Pittsburgh Study. Dotted lines represent pressures of 'control' populations (see text).

carbohydrates is not borne out by these studies.

The cumulative distribution of initial blood pressures measured in the arm with the subject sitting is presented in figure 5. Both the obese males and females had the same distribution of diastolic blood pressures, although the females had higher systolic pressures, a trend also noted in healthy populations to a lesser extent (7, 21). The dotted lines represent the distribution of blood pressures in healthy populations of the same age (21). Our obese subjects are clearly more hypertensive than the 'controls,' as has been noted in other studies (18). In fact, if one accepts 100 mm Hg diastolic pressure as being the dividing line between normotension and hypertension (21), approximately 8% of normals and 35% of obese individuals in our study are hypertensive.

The distribution of serum cholesterol in our obese population is shown in figure 6. The median value for females was 246 mg % and for males 254 mg %. The curves for both obese men and women are displaced to the right, i.e. the hypercholesterolemic side of the distribution curve obtained in the cooperative study of the U. S. Public Health Service (22) for healthy males of the same age group (40–59 years). Average serum cholesterol values for other middle-aged American populations subsisting on similar diets show variation from 225 to 255 mg % (23–25), so that the extent to which our obese population is truly hypercholesterolemic is not clear. Keys (26) found no relationship between serum cholesterol and relative body weight in Minnesota businessmen.

The prevalence of five major illnesses in 164 of our subjects is shown in figure 7. As indicated previously, about 35% have hypertension. Approximately 18% have heart disease of some kind, of which half is coronary artery disease as indicated by medical history and electrocardiogram. Fourteen per cent have a history of acute cholecystitis, cholecystectomy or a positive Graham test. Arthritis was noted in 8% and diabetes in 6% of this population. Although these are preliminary data, they indicate the extent to which this population has the chronic illnesses commonly associated with obesity.

EFFECT OF DIET THERAPY ON HEALTH

Following their initial evaluation, each subject in our study was instructed in one of three diets in accord with a prearranged plan. In these diets, the calories varied from 1000 to 1700 and fat from 40 to 90 gm/day. Although 80% of those admitted to the study were in attendance at the clinic during the first 6 months of follow-up, this figure had dropped to 38% by the end of the second year. The data presented below represent only a partial

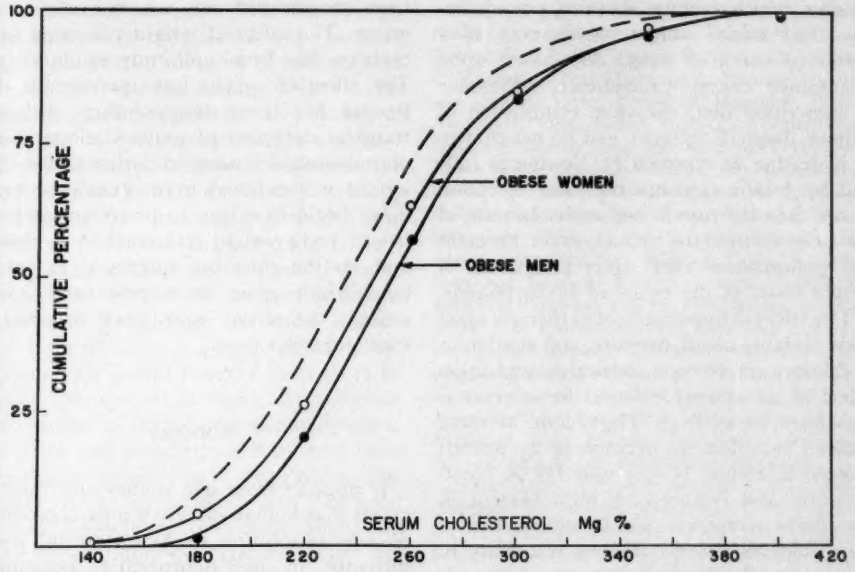

FIG. 6. Cumulative distribution of serum cholesterol in obese men and women and non-obese men 40–59 yr. of age. Open circles indicate values for women and closed circles indicate values for men in the Pittsburgh Study. Dotted lines represent the values obtained in the U. S. Public Health Cooperative Study of Lipoproteins and Atherosclerosis in healthy males 40–59 yr. of age (all populations but Los Angeles which appeared atypical) (22).

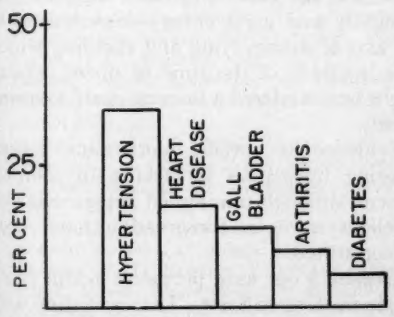

FIG. 7. Prevalence of chronic diseases in obese men and women 40–59 yr. of age. This represents an analysis of 164 cases from the Pittsburgh Study.

analysis of the findings of the study and will be confined to a description of the effects of prescribing diets containing 1000 cal. and 40 gm of fat (36% cal.) to obese women, 40–59 years of age, averaging 210–220 pounds in weight.

The failure to obtain sustained weight loss in patients given reducing diets has long been recognized. Table 2 presents the weight changes in a group of 24 women followed for 18 months. Dietary histories were taken at 6-month intervals after instruction of the therapeutic diet in order to evaluate adherence to the regimen. The energy 'expended' is then calculated from the dietary record plus the observed weight change. Although these calculations are crude, they illustrate the trend toward less expenditure of energy with dieting and weight loss, a phenomenon also noted by Young *et al.* (27) and Keys and Brozek (1). Similar results have been obtained by direct measurement of energy exchange of obese individuals undergoing weight reduction on our metabolic unit. The inevitable 'plateau' in weight which occurs in most obese individuals after a period of dietary restriction appears to be due in part to an attenuation in energy output plus the arrival at a dietary 'floor,' which, for emotional reasons, is the minimum food intake which they can tolerate for prolonged periods. This intake averages about 1250 cal. in the obese women we have studied. On these intakes, they come into caloric equilibrium at new and lower

weights, which average about 25 pounds below their initial weight. Attainment of a predicted curve of weight loss based upon maintained energy expenditure, adherence to prescribed diet, exclusive combustion of adipose tissue (8 cal/gm), and no net change in hydration as reported by Newburgh (28) and by Jolliffe (29) has been the exception rather than the rule in our study. In most of our cases, further, the 'reducing diet' becomes the 'maintenance diet' upon attainment of weight losses in the range of 20–80 pounds.

The effect of hypocaloric diet therapy upon body weight, blood pressure and symptoms of dyspnea on exertion, arthralgia and upon mood of 44 women followed for 2 years is presented in table 3. Thirty-four of these subjects who lost an average of 25 pounds showed a decline of 9/4 mm Hg in blood pressure, and reported an improvement in the above symptoms and in mood. Ten of these subjects either remained stationary in weight or gained weight because of non-adherence to the diet therapy. They showed essentially the same decline in blood pressure and improvement in mood, but no change in symptoms attributable to exertion. The positive effects of weight reduction upon blood pressure claimed by some (18, 30) have not been impressively demonstrated in most patients in our clinic. Likewise, the 'dangers' of reducing in terms of depression and even more severe psychiatric disorders (31) have been encountered only uncommonly in our group. The effect of weight reduction upon diabetes has been uniformly salutary (32). The effect of weight loss upon serum cholesterol has been disappointing. Although transient decreases in serum cholesterol and phospholipid following initiation of diet therapy have been noted, in most cases the serum lipids begin to return to pretreatment levels before body weight has reached a plateau and by the time the subject is in caloric equilibrium again at a new (and lower) weight, the serum lipids have returned to their control values.

TABLE 2. WEIGHT LOSS AND ESTIMATED CALORIC EXPENDITURE OF 24 MIDDLE-AGED SUBJECTS ON A REDUCING DIET

Time, mo.	Wt.	Diet RX Cal.	Cal. Intake	Cal. Expen.	Cal./M²/hr.
0	217	ad lib.	2,030	2,030	42.2
6	198	1,000	1,250	1,626	35.4
12	193	1,000	1,225	1,324	29.0
18	192	1,000	1,110	1,130	24.7

SUMMARY

It appears from our studies and those of others that human obesity is a psychosomatic disorder of multiple etiology featuring a disturbance in the homeostatic mechanism matching food intake to energy expenditure at normal insight. The fact that many middle-aged obese persons demonstrate food intakes which are euphagic or even hypophagic when compared with normal weight controls of the same sex, age and occupation, suggests that inactivity and good energy conservation in the acts of sitting, lying and standing which take up 80% of the time of obese persons might be considered a 'somatic trait' favoring obesity.

Evidence for specific biochemical lesions favoring lipogenesis is lacking in man at present although diminished ketogenesis and excellent nitrogen conservation have been demonstrated.

Obesity is our most prevalent health problem in the United States. The association with it of atherosclerosis, diabetes, hypertension and cholecystitis makes it a sign of vulnerability to these illnesses.

TABLE 3. EFFECT OF DIET THERAPY UPON SYMPTOMS, BLOOD PRESSURE AND BODY WEIGHT OF 44 OBESE WOMEN FOLLOWED FOR A 2-YEAR PERIOD

Group	Nr.	Body Weight			Blood Pressure			Symptoms		
		I	F	Δ	I	F	Δ	Dyspnea	Joints	Mood
Losers	34	207	182	−25	148/92	139/88	−9/4	I*	I	I
Control	10	219	225	+6	152/89	143/89	−9/0			I

* I = Improved.

The treatment of obesity with diet therapy —and that is the only useful way—is beset with pitfalls. Only a minority of patients ever reach 'desired' or even average weight under such a program because the two factors of attenuation of energy expenditure and psychological need for food soon obliterate the negative caloric balance established by initial adherence of the obese subject to the prescribed diet. It has been found, further, that clinical and biochemical signs of disease and disordered function do not, with the exception of the glucose tolerance, impressively improve over a 2-year period in association with weight losses of from 10 to 80 pounds. On the other hand, symptomatic improvement as regards exertional dyspnea, joint pains and mood is noted in most cases experiencing weight loss of this degree. The ultimate extent to which health has been improved by weight reduction in our group will be decided only by long-term follow-up.

The author acknowledges the important collaboration of the following persons: *Physicians*: Harry F. Bisel, Robert Blume, Jerrold D. Hydovitz, William F. Kremer, Albert Marrangoni, Emanuel Stadlan and John W. Vester. *Psychiatrist*: Marvin R. Plesset. *Nutritionists*: Elena Becker, Juanita A. Eagles, Doris Longman, Marcia Riegl and Ruth Roth. *Dietitians*: Janice Neville and Nora Vallano, with the assistance of some 30 volunteer dietitians from the Pittsburgh Dietetic Association. *Head Nurses*: Catherine Frasca, Bernadette Halloran and Veronica Stezoski. *Biochemists*: John Jablonski, Edmund Taylor, Senophia Gary and Blendena Duncan. *Medical Technologists*: Margaret Rainwater and her staff. We are indebted to the J. B. Roerig Company, New York City, and the Upjohn Company, Kalamazoo, Mich., for ample supplies of vitamin supplements. Original work cited herein supported in part by grants-in-aid from American Dairy Association, Chicago, Ill.; Greater Pittsburgh Dairy Industry Association, Pittsburgh, Pa., Howard Heinz Endowment, Pittsburgh, Pa., National Dairy Council, Chicago, Ill.; Upjohn Company, Kalamazoo, Mich.; U. S. Public Health Service (H-2258), Bethesda, Md.; and Western Pennsylvania Heart Association, Pittsburgh, Pa.

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Advances Related to Diabetes

ALEXANDER MARBLE

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IN THE 36 YEARS since insulin was made available for general use, it has transformed the lives of hundreds of thousands of persons with diabetes all over the world. Prior to 1922 treatment with a low-calorie diet and resulting undernutrition had brought about some slight improvement in life expectancy but, despite this, in a series of 836 patients dying between 1914 and 1922 the average age at death was only 46.7 years and the average duration of diabetes was only 6.1 years. The insulin era has produced such a change in prognosis that in the same clinic from which the above statistics are quoted, among 640 patients dying between January, 1956 and December, 1957 the average age at death was 64.7 years and the average duration of diabetes 18.2 years (table 1). In fact, in this group of 640 patients the average duration of life after onset of diabetes was considerably greater in the younger age groups, being 26.4 years for those with onset at 0–9 years, 23.5 years for those with onset at 10–19 years and 25.1 years for those with onset at 20–39 years.

Impressive though these figures are, they err on the side of being conservative since they are based on fatal cases and do not take into account the vast numbers of patients who are living on and on and in many instances surviving longer with diabetes than, according to mortality tables, they would be expected to live without it. The number of patients with diabetes of 30–35 or more years' duration is growing steadily. Furthermore, the cold statistics of mortality and life expectancy tables do not bring out the fact that along with lengthening of years there has come such improvement in general health and capacity for work, recreation and family life that the diabetic who has kept his disease under control has been able to live, for all practical purposes, almost as happily and as usefully as the nondiabetic. These results in the clinical field have been matched and usually preceded by discoveries and advances in research in the laboratory. In the discussion which follows, certain of these developments, both in the laboratory and clinic, will be discussed briefly.

INCIDENCE

That diabetes is a universal disease affecting people of all races, living in all climates and under all conditions is generally conceded. Not so well recognized but probably true is that diabetes occurs about as frequently in one country and in one climate as another providing certain influencing factors are kept in mind. The incidence of diabetes is greatest in those populations *a*) in which the average age of people is oldest, since the onset of diabetes is usually in middle life and particularly in the decade between 45 and 55 years and *b*) in which generous overnutrition favored by a less active physical life leads frequently to obesity. There is evidence of a higher incidence of diabetes in certain racial groups but this may well be related to intermarriage and accentuation of a hereditary predisposition. If this be so, the apparent influence of race may be expected to diminish with increased capabilities of travel and the shifting of population groups which are so characteristic of the present day.

The above comments refer to the true incidence of diabetes. On the other hand, published statistics are influenced markedly by the efficiency of diagnosis, the accessibility of medical care to the entire population and the methods employed and effectiveness of recording and tabulating of statistics regarding morbidity and mortality. Consequently, at the present time published figures can by no means be taken at face value and the inference is strong that if the various factors

TABLE 1. AGE AT DEATH AND DURATION OF DIABETES
(Experience of Joslin Clinic*)

Period	No. of Deaths	Average Age at Death	Average Duration of Diabetes
		yr.	*yr.*
1897–1914	326	44.5	4.9
1914–1922	836	46.7	6.1
1922–1936	4138	61.2	9.5
1937–1949	7739	65.0	13.0
1950–1955	4376	64.7	15.6
1956–1957	640	64.7	18.2

* Data compiled with the cooperation of the Statistical Bureau, Metropolitan Life Insurance Company.

just mentioned are taken into account, many of the discrepancies in incidence between one country and another tend to disappear.

Surveys in recent years have indicated that even though ordinary care may be used in the detection of diabetes, many individuals with the disease may remain undiagnosed unless routine examinations of the blood and urine for sugar are made. In one of the earliest studies, Wilkerson and Krall (1) of the United States Public Health Service carried out in 1946 urine and blood tests in 70% of the total population of Oxford, Massachusetts, a town of about 5,000 persons at that time. In this extensive survey they found 70 cases of diabetes, 40 previously known and 30 newly discovered. From their results they estimated that the prevalence of diabetes in Oxford was 1.7%. Surveys in other areas since then have yielded quite similar results. If one uses this figure, the total in the United States would amount to about 3 million persons, a number much greater than that of earlier estimates.

To find the 'million hidden diabetics' has been a major objective of the American Diabetes Association during the last several years. A nation-wide 'Diabetes Detection Drive' was launched in 1948 with the purpose of interesting physicians and the public in discovering and bringing under treatment those persons who have diabetes but who are either not aware of it or are neglectful of their condition. This has been a continuing project during the past 10 years and in 1958 the annual 'Diabetes Week' will be held throughout the United States during the week of November 16–22. Emphasis is laid on the fact that in the search for unknown diabetics one does best to concentrate on persons who have a diabetic relative, are above the age of 40 and are overweight. As time has gone on, the emphasis of the program of the American Diabetes Association has been increasingly on the feature of education of the public regarding diabetes, using the detection drives as a means to that end.

PHYSIOLOGY

In the diabetic man or animal the metabolism of carbohydrate is abnormal in that, depending upon the severity of the disease, glucose is, to a greater or less extent, not utilized in the tissues or stored as glycogen or fat in a normal manner but instead accumulates in the blood and is excreted in the urine. Hyperglycemia and glycosuria occur in the diabetic subject even though fasting. The body prefers glucose as a source of energy but when the utilization of carbohydrate is impaired, protein and fat are called upon to an unusual degree. The body is sparing in its use of protein but in the severely diabetic individual there is increased breakdown of this foodstuff as reflected in the high nitrogen excretion in the urine. It is true that in the normal person the combustion of fat plays an important role in continuing metabolism and the ketone bodies which result from the breakdown of fat are oxidized to furnish energy, but in the uncontrolled diabetic the amount of fat catabolized may be so great that the quantity of ketone bodies produced exceeds that which may be used. These flood the organism; the end result is ketoacidosis, which, if unchecked, leads to coma and death.

The miracle is that by the parenteral injection of appropriate amounts of insulin this whole abnormal process may be corrected. The gross events are relatively easy to demonstrate and, in fact, are seen many times daily in the treatment of diabetic patients. However, a multitude of investigations carried out all over the world since 1922 have only partly supplied the answer to key questions which, on the surface, seem quite simple. What is the basic defect in diabetes? What is the mode and site of action of insulin? On the other hand, optimism is warranted because in recent years great strides have been

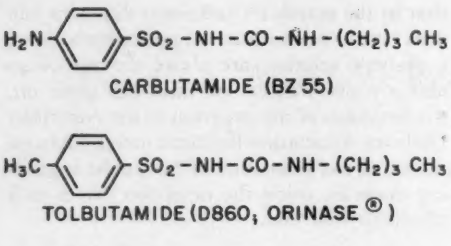


FIG. 1. Formulas for 3 sulfonylurea compounds.

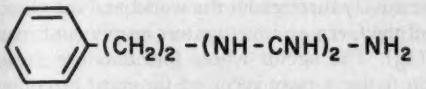
made in the understanding of these fundamental problems. In this brief essay, mention of only a few of these advances in knowledge may be made.

a) Metabolic integrations. There is abundant evidence to indicate that the metabolism of carbohydrate, protein and fat do not proceed in separate and distinct compartments but rather that there is a common 'metabolic pool' which is entered usually at the 2- or 3-carbon unit stage and which serves as a common pathway of final oxidation and degradation and also as a link which permits ready interconversion of biological constituents according to the needs of the organism. Obviously diabetes cannot be thought of as a disease which is concerned with carbohydrate alone. The synthesis of long-chain fatty acids by either liver or adipose tissue from precursors such as pyruvate, is almost completely suppressed in uncontrolled diabetes. In addition, fatty acid mobilization and catabolism are markedly increased. Furthermore, it is well-established that in the diabetic state there are decreased protein synthesis and increased protein breakdown to amino-acids.

b) Mechanism of insulin action. The studies of Levine *et al.* (2), Park and Johnson (3), Ross (4) and others have led to the concept that insulin exerts at least part of its action by facilitating the passage of glucose through certain cell membranes, particularly those of muscle and adipose tissue. Once having been admitted to the interior of the cell, inert glucose is ready for phosphorylation and thereby conversion into a form which is metabolically active. In contrast to muscle and fat, in certain tissues such as those from the brain, kidney and intestinal mucosa, the cells appear to be freely permeable to glucose even in the absence of insulin. The situation as regards the liver is not entirely clear. Whereas liver cells seem to be permeable to glucose in the absence of insulin, there are many well-documented effects of insulin in the correction of abnormalities in the liver as demonstrated in the intact animal.

c) Determination of insulin in blood. For a long time there has been sensed the need and desirability of a method by which the amount of insulin in the blood might be measured. Attempts along this line have been made by various workers. Among these have been Bornstein (5) by using induced hypoglycemia in specially prepared cats and mice as an index; Vallance-Owen (6), Randle (7) and Groen (8) by measuring glucose uptake by the isolated rat hemidiaphragm; and Balmain *et al.* (9) by determining gas formation by the mammary gland of the lactating rat. These techniques leave much to be desired in the way of ease of accomplishment, sensitivity and reproducibility. More recently Renold and co-workers (10) have devised a procedure to measure insulin-like activity which is based on the finding that insulin added *in vitro* to rat epididymal fat results in a four-fold increase in glucose uptake and an eight-fold increase in the oxidation of glucose-1-C^{14} to $C^{14}O_2$ (11). Using this technique, quantities of insulin as small as 0.00001 U/ml. may be measured. Already worthwhile data have been obtained, giving rise to the hope that continued work may yield results of interest and great value both in the laboratory and in the clinic.

d) Unesterified fatty acids in blood or plasma. That blood lipids, ketogenesis and carbohydrate utilization have important interrelationships has long been appreciated. Recently, however, an especially significant fraction of blood lipids, the unesterified fatty acids ('UFA' or 'NEFA'), has been the object of much study and a new field of investigation has opened up. Dole (12) and Gordon (13) have introduced methods for the determination of that fraction of fatty acids which is carried in the blood stream as an unesterified fatty acid-albumin complex. This fraction, although relatively small, is highly active in a metabolic sense and has a short turnover time. Unesterified fatty acids are elevated



PHENETHYLBIGUANIDE

FIG. 2. Formula for phenethylbiguanide (Phenformin). This compound was released for sale under the trade name of DBI (U. S. Vitamin Corp.) in March, 1959.

in inadequately controlled diabetes. The giving of insulin and glucose causes a prompt decrease which apparently parallels glucose utilization. Hence the determination of the unesterified fatty acids may serve as an index of underlying metabolic events and may well prove to be useful clinically particularly if it becomes possible to shorten the time and labor involved in carrying out the procedure.

TREATMENT OF DIABETES

The basis of the successful management of diabetes continues to be a restricted, though adequate, diet which is followed consistently. The restriction must be greatest in carbohydrate with prescriptions for adult patients ranging from about 150–200 gm/day. As compared with older practices, these allowances of carbohydrate are relatively liberal and experience has demonstrated the advantages of such. So-called 'free diets' or diets containing 300 or more grams of carbohydrates daily enjoyed a certain vogue in some quarters in recent years but experience has shown that these often amount to no dietary regulation whatever, making satisfactory control of diabetes exceedingly difficult if not impossible. Protein must be allowed in truly adequate amounts, usually about 1 gm/kg of ideal body weight, and in young, rapidly growing children the quantity may reach 3 or even 4 gm/kg. The rest of the caloric needs must be supplied by fat and in the adult the amount of this foodstuff ranges usually from 60 to 100 gm/day. It goes without saying that all features of the diet must be adjusted according to the age, sex, weight, body build, physical activity and the dietary likes and dislikes of the patient concerned. Often it must be altered in accordance with special indications arising from accompanying disease states.

In this connection it must be pointed out that data published in many texts give erroneously high values for carbohydrates and calories supposedly taken by normal persons in the general population. If one tabulates and calculates the composition of food eaten by middle-aged and elderly persons, one finds that a large segment of the population naturally selects diets containing less than 250 gm of carbohydrate and less than 2,000 cal. daily. Certainly the average middle-aged diabetic woman who engages in light physical activity maintains her weight and strength on diets yielding 1600–2000 cal. daily. Even with men it is rarely necessary to provide more than 2000–2500 cal. unless the individual concerned leads a life calling for strenuous physical exertion. These comments are particularly valid in present-day United States in which most jobs are mechanized to such a degree that sustained, hard, manual labor is unnecessary.

In recent years there has been much attention paid to the possible harmful effects of saturated fats in the production of hyperlipemia, hypercholesterinemia and atherosclerosis with resulting vascular disorders. Evidence is available to indicate that the use of diets in which fats are chiefly or totally of unsaturated type may bring about lowering of blood cholesterol and clinical improvement. However, such diets are often bizarre in type, unpalatable and difficult for the patient to follow. From the standpoint of the practicing physician treating diabetic patients, it would seem unreasonable today, in the light of available knowledge, to advocate any radical change in the composition of diets as regards type of fat. The body's ability to synthesize cholesterol must be kept in mind. However, the following guiding principles appear logical: *1*) The total fat and calories should be kept at that level for a given individual which will prevent obesity or correct such, if already present; *2*) insofar as practicable, unsaturated fats should be chosen rather than saturated fats. Vegetable fats are more likely to be unsaturated than are those of animal origin but not necessarily or uniformly so. More stringent rules must await the accumulation of further data to indicate that such are necessary.

Steady advances have been made in the development of newer types of insulin designed to make treatment more convenient and more effective. The latest addition is

TABLE 2. CAUSES OF DEATH IN 691 PATIENTS WITH ONSET OF DIABETES UNDER THE AGE OF 15 YEARS
(Experience of Joslin Clinic*)

Period	1898–1922	1922–1936	1937–1943	1944–1949	1950–1955
Cause of Death	Per Cent				
Coma	86.0	56.6	27.2	9.7	5.7
Coronary ht. dis.			2.5	10.4	10.0
Nephropathy		2.0	12.3	36.8	57.1
Cer.-vasc. accid.			1.2	2.1	5.2
Infections†	6.4	23.2	24.7	6.9	7.6
Tuberculosis		8.1	9.9	11.1	2.4

* Data compiled with the cooperation of the Statistical Bureau, Metropolitan Life Insurance Company.

† Excluding tuberculosis.

the lente family of insulins which include three types, lente, semi-lente and ultra-lente (14). Some types of insulin are more adaptable and usable than others but all insulins are effective and can be used successfully if due regard be taken on the one hand, for the rapidity of action and duration of effect of the type used, and on the other hand, for the character of the diabetes of the patient under treatment.

Oral hypoglycemic agents. Despite the great effectiveness of insulin and despite the revolution created by it in the outlook of the diabetic, there has been a constant desire for a preparation which could be taken by mouth. Attempts to employ insulin orally have not met with success because of inability to prevent its breakdown in the digestive tract, with consequent loss of potency. Various herbs and vegetable extracts have shown some hypoglycemic action under certain conditions but in no instance have the effects been significant enough to warrant the use of such preparations in the treatment of diabetes. Synthalin was used for a few years in the 1920's but abandoned because of toxic effects on the liver and kidneys. It was, therefore, with much interest, albeit considerable skepticism initially, that reports were received from Germany in 1954 and 1955 regarding the blood-sugar-lowering properties of a sulfonamide referred to originally as BZ55 and subsequently in the United States as carbutamide. Since that time this and other sulfonylurea compounds have been used extensively throughout the world and the claims of the German investigators amply confirmed (15). The agents whose formulas are shown in figure 1 have received the most attention. A large number of related compounds have been prepared and studied; among these, one known as meta-hexamide is now receiving clinical trial.

The sulfonylurea compounds lower the blood sugar in nondiabetic individuals and in certain middle-aged and elderly persons with 'mild' diabetes. They are not effective in those patients with onset of diabetes in childhood and early life or in those older persons whose diabetes is of the unstable, juvenile type. Most responsive patients are those with onset of diabetes above the age of 40 years and whose insulin requirement is below 40 U, and more particularly below 20 U, daily. The sulfonylurea compounds are not effective in keto-acidosis and coma, in acute infections, especially with fever, or during and following major surgical operations. The only preparation commercially available as yet is tolbutamide (Orinase).[1]

Despite many investigations, there is still much controversy regarding the mode and site of action of the sulfonylurea compounds. There are data which suggest that they act, at least in part, on the pancreas to stimulate the production and release of insulin. This implies that the agents would be effective only in those subjects who possess a pancreas with beta cells capable of such response and such, indeed, fits in with laboratory and clinical experience. A second site of action appears to be in the liver in which the compounds reduce the amount of glucose released into the blood either by inhibitor effect on certain enzyme systems or by action of endogenous insulin secreted in response to the drug. Evidence that sulfonylurea agents promote peripheral utilization of glucose directly as insulin does is lacking or, at best, equivocal.

As might be anticipated, the unwise use of medication by mouth by patients unresponsive to the sulfonylurea compounds must be carefully avoided. Those with the more severe grades of diabetes may develop keto-acidosis and coma on omission of insulin and attempted substitution of an oral agent. Others, though not becoming acutely ill, may achieve

[1] Chlorpropamide was released for sale under the trade name of Diabinese (Pfizer) in November, 1958.

only fair or poor control of diabetes with the risk of development of disabling complications over a period of years.

In addition to the sulfonylureas, one other class of compounds, the biguanides, have been subjected to clinical trial during the last 2–3 years. These consist of phenethylbiguanide (DBI) and its analogues. These compounds lower the blood sugar in certain responsive diabetic patients, including children. In adults with a low insulin requirement, satisfactory control of hyperglycemia and glycosuria may be obtained by use of the drug alone. In children, almost without exception, it is necessary to give some insulin along with the biguanide. There is some evidence to suggest that in some patients the biguanides, by lowering the insulin requirement and perhaps by other unidentified means, may render somewhat smoother the course of unstable diabetes and reduce the tendency to insulin reactions (16).

It is too early to assess the place of the oral hypoglycemic agents in the management of diabetes. Certain questions are relevant—By controlling hyperglycemia and glycosuria, is the basic metabolic defect in diabetes corrected as with insulin? Will the administration of the chemical agents over many years lead to toxic effects not apparent so far? Will the use of the drugs over many years protect the patient from late sequelae of diabetes as well as insulin? Further study and the passage of time are required to answer these questions.

LATE COMPLICATIONS AND THEIR PREVENTION

During the insulin era the incidence of, and mortality from, diabetic coma have fallen remarkably. Furthermore, with the help of modern antimicrobial agents, deaths from infections and from surgical complications occur much less commonly. The greatest problem and the greatest challenge at the present time are the late sequelae of diabetes affecting especially the vascular and nervous systems. These complications may be found to a greater or less degree in persons of all ages with long-term diabetes. However, they are most tragic when they occur in severe grade in patients in the fourth and fifth decades of life who after 15, 20 or more years of diabetes are afflicted with retinitis which may seriously reduce vision, hypertension, vascular sclerosis and chronic renal disease. Often such patients will have had symptomatic neuropathy at one time or another during the course of diabetes. In this group of relatively young persons death occurs most commonly in renal failure. The changing incidence in the causes of death among patients with onset of diabetes in childhood is shown vividly in table 2.

Once these complications have become established, treatment is relatively unsatisfactory. The greatest hope lies in prevention or, at least, postponement of these unpleasant sequelae. Studies of patients with onset of diabetes under the age of 25 years have demonstrated quite conclusively that the deciding factor is the degree of control of diabetes. Duration of diabetes is important largely because it allows a greater length of time during which deleterious influences may exert their influence. Those patients with consistently good control of diabetes have, after 15 or more years, the fewest and least severe degenerative changes (17). Contrariwise, those with poor control suffer the most distressing sequelae of long-standing diabetes. Careful, continuous control must be the constant aim of those entrusted with the care of patients with diabetes.

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Summary

W. HENRY SEBRELL, JR.

Columbia University

THIS PROGRAM has been a contribution toward answering the question—Is there a nutritional defense against degenerative disease? We have had excellent discussions of atherosclerosis and coronary artery disease, obesity and diabetes. These were selected because they are among the most important of the degenerative diseases and they illustrate excellently the complications and interrelations in making application of the nutritional knowledge we have to the control of degenerative diseases.

One of the purposes in introducing the population figures in the introduction to this program was to point out that infant mortality is not nearly so great a problem in this country as it is in many other countries, and a high infant mortality rate is one of the serious results of malnutrition. Our malnutrition in this country is of a different type. It is the malnutrition of overabundance rather than insufficiency. It is the relation of this type of malnutrition to the chronic and degenerative diseases which presents the intricate problems which have been so ably presented by our speakers this afternoon.

There is a nutritional defense against degenerative diseases if we mean by defense the prevention or delaying in the onset of degenerative diseases. However this defense is neither a pill nor a prescription. The answer, as this program has shown, is a lifetime of good eating habits. This—in effect—is our nutritional defense against degenerative diseases.

WORLD-WIDE CONTRASTS AND PRACTICAL PROBLEMS

Introduction

ERIC K. CRUICKSHANK

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I HAVE HAD THE PRIVILEGE of knowing two of our speakers this morning for some time. I can assure you that they are ably equipped to discuss this morning's problem—the global aspects of nutrition and the contrasts thereof.

In fact, much more so than I am to chair such a discussion because I am not, fundamentally at least, a nutritionist. I am an internist with a special interest in nutrition and my interest in nutrition was gratuitous and rather personal in the first instance. I was unwillingly thrust into the field in that I became a 'guest' of the Japanese some 15 years ago and for 3½ years thereafter, I was able to study human malnutrition at first hand!

But it was a fascinating opportunity to study an enormous group of young men—some 80,000—the majority initially in good health, when they were brought into a camp where a large medical staff could look after the medical aspects of their problem, at least from a diagnostic and observational point of view. Therapy, as you can imagine, was negligible.

During these 3½ years we had the opportunity of watching various deficiency syndromes develop under relatively controlled conditions, conditions probably more nearly approximating the laboratory than mankind has been able to do in the past, and let us hope never has to do again. Nutrition has remained one of my first loves since then, in spite of the disadvantages of my initiation.

I also have had the opportunity of continuing this work in Jamaica over the last 8 years, and I couldn't ask for a better plant and personnel. As perhaps some of you know, it is a country of contrasts—hills and valleys, hurricanes and sunshine, the rich, well-fed north coast tourists and mothers with malnourished children in the more remote districts. It is from these latter that I have been able to draw my recent experience in the nutritional field.

Moreover, it is, I think, a pilot area where all the problems of the world are to be found in miniature—problems of race, social and economic struggle, of limited economy, of an expanding population, and to be there at this time and to be able to take part in this mass experiment that was being thrust upon us is, I think, my privilege.

However, its problems are negligible compared with these that are facing wide areas of Asia, Africa, Central and South America, and it is of these problems and how they are being tackled, that we are to hear today.

Malnutrition—a Global Problem

JAMES M. HUNDLEY[1]

Food and Agriculture Organization of the United Nations

MY DISCUSSION will have three purposes: *1*) to review hastily the evidence indicating that malnutrition is an important global problem; *2*) to examine a few of the fundamental causes of malnutrition; and *3*) to make a few points about the practical possibilities of eliminating nutrition problems.

I must emphasize that the target of my remarks will be the so-called underdeveloped world. This is a vast area with many different problems and many different conditions. I will have to speak in generalizations to some extent. There are always exceptions to generalizations, so I hope you will grant some poetic license.

The assumption is often made that because a population is rural and, from our standpoint, uneducated and primitive, it is therefore malnourished. This is not necessarily true. We had this brought to our attention again by a study done in French West Africa. A group there wished to find a population with a low protein diet that might be suitable to study the beneficial effects of protein supplementation. After much careful study four villages in the interior of French West Africa were selected. A baseline nutrition survey was done. This survey was done during what are called in Africa the 'hungry months;' these are the months just before the new harvest comes in, and generally malnutrition should be at its worst. The findings of this survey were quite unexpected. Intake of calories and essential nutrients exceeded estimated requirements, sometimes by substantial margins, except for riboflavin which was borderline in some of the diets. Clinical and laboratory examinations in general confirmed the dietary findings indicating relatively good nutrition (1).

On the other hand, evidence indicating that malnutrition is an important global problem can be divided into two classes of evidence. First is what might be called presumptive or suggestive evidence. For example, there are a number of statistics that can be used to indicate the probability of malnutrition. Maternal mortality, infant mortality, mortality in the age group 1–4, and growth rates are probably the most useful of these for nutrition purposes. For example, in infants under 1 year mortality rates in 3 well-developed countries selected at random—Sweden, Switzerland and England—ranged from 18 to 28 per thousand. In 3 underdeveloped countries—Egypt, Mexico and Brazil—they ranged from 94 to 208—5–10 times higher; but even more striking, in the age group 1–4 where nutrition hazards are especially severe, mortality rates in these 3 well-developed countries ranged from 1.0 to 1.6, and in the same 3 underdeveloped countries from 16.2 to 49.7, 10–40 times higher (2).

These types of statistics have many serious limitations. Aside from their reliability, the main problem is that none of them are specific with respect to nutrition. They reflect the sum total of the effects of disease, environment and many other factors, including nutrition.

Another type of presumptive or suggestive evidence comes from national food production statistics, the FAO Food Balance Sheets being a well-known example. For example, India, Indonesia and the Philippines show an average per capita consumption of calories ranging from 1700 to 2177. This is in contrast to the average per capita consumption of calories in most western countries of around 3000 (3).

The same picture can be derived from protein supplies. These same 3 underdeveloped

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countries have protein supplies in the range of 40–50 gm/day, whereas 80–100 gm/day would be more typical of the well-developed countries.

Again, however, national food production and consumption figures have limited usefulness because they conceal several important facts. High-quality protective foods are generally more expensive and tend to be consumed by the economically privileged. Therefore, a corresponding lesser amount goes to the economically underprivileged.

Secondly, national food supplies often suggest a quite varied diet. However, diets within regions of a country are usually much more restricted because of inadequacies in transport, storage, refrigeration and economics. For example, the national food supplies of Brazil suggest a varied diet. However, in the Amazon, in the northeast, cassava is the staple; in the central zone of Brazil it is maize; in the southern zone a much more varied diet with meat, fruit and vegetables is available (4).

The third limitation of national food production and consumption figures is that they conceal the fact that there are often seasonal surpluses of food followed by seasonal shortages of food. These become the 'hungry months' referred to earlier.

These types of indirect evidence must be supplemented by some more specific information from nutrition surveys. Such surveys are being done on a steadily expanding scale. There are now voluminous data from many countries. At times, these surveys have revealed a nutrition situation better than would have been expected from national food supplies. For example, it was stated earlier that in India the average per capita calorie intake is about 1710, with 47 gm of protein; yet 92 surveys done at various times in various places in India revealed a calorie intake between 2000 and 3000. In 28 surveys, it was between 3000 and 4300. In only 17 surveys were calorie intakes as low as 1100–1500 (6).

The average protein intake in 132 surveys in India was 73 gm as contrasted to an average of 47 shown in the food balance data. Such surveys show clearly the great regional and socio-economic differences in various parts of the country.

On the other hand, nutritional surveys sometimes show a worse situation than one would expect from national food supplies. In parts of Southeast Asia—Thailand for example—one would expect no particular problem with beriberi based on food produced and presumably consumed. Yet nutrition studies show that there is a beriberi problem due principally to the fact that rice is overmilled, thus removing most of the thiamine and what little remains is washed away through cooking (5).

As another example, one would not expect a severe vitamin A problem in the trust territory of Ruanda-Urundi, since their diet contains a reasonable amount of vitamin A active substances almost entirely in the form of carotene (7). It has been shown very recently that due to the very low amount of fat in the diet the carotene is not absorbed. Consequently, there is very widespread evidence of vitamin A deficiency (8, 9).

Some nutrition surveys have revealed quite alarming evidences of malnutrition. In South India a quite recent study showed that 10–16% of hospital admissions were for kwashiorkor (10). Gross retardation of growth, uniform low hemoglobin, changes in serum protein, skin and hair changes, liver enlargement and signs of vitamin A and riboflavin deficiencies were noted very frequently in nonhospitalized children.

Another slightly different type of survey, done in a village not far from Dakar in French West Africa, also showed a very alarming picture. The infant mortality rate in this particular area was well over 200. Fifty-three per cent of the children in the 1–2-year-old age group showed evidence of kwashiorkor. Liver biopsies done on 200 children showed 15% with cirrhosis of the liver. Rickets, pellagra, scurvy, thiamine or riboflavin deficiency signs were found in from 2 to 10% of the children (personal communication from Lt. Col. Raoult).

On the other hand, in villages not more than 200 km distant from this particular area, 996 children to age 12 were examined, with only 3 showing evidence of early kwashiorkor and none with outspoken evidences of the disease (1).

In Indonesia, quite recently, Darby and McLaren (11) made a study which showed a very alarming incidence of xerophthalmia in infants and preschool children, with a

quite high percentage of those afflicted becoming totally blind. In Formosa, Jolliffe and Tung found 70% of school children with evidence of riboflavin deficiency, and lesser percentages showing evidence of thiamine, iron, vitamin A and niacin deficiencies (12).

In general, recent nutrition surveys have indicated that the main deficiencies are as follows: *1. General undernutrition.* This condition arises mainly from simply not having enough to eat, i.e. chronic semi-starvation. We as nutritionists often become so preoccupied with the rather exotic deficiency disease syndromes that we overlook this simple fact. Almost irrespective of the quality of the diet, if there was simply more to eat many nutritional problems would disappear. *2. Protein malnutrition.* The second most prevalent and serious deficiency undoubtedly is protein malnutrition. This is an instance where quality of the diet is very important. Other speakers will cover this topic. *3. Anemia.* This is particularly prevalent in mothers and young children. In places it seems to be caused by iron deficiency, at times complicated by endemic diseases. At other times, protein and calorie deficiency seem to be involved. *4. Vitamin A deficiency. 5. Riboflavin deficiency.*

These last two seem to be prevalent throughout practically all of the underdeveloped world, varying in severity, of course, from area to area.

Other deficiencies such as beriberi, pellagra, scurvy and rickets occur, and in certain regions in rather severe form, but on a global basis they are less prevalent and less deleterious to health than the 5 types of deficiencies already mentioned.

As to the causes of malnutrition, one can, for purposes of discussion, dissect out quite a number of distinct fundamental causes. However, one must remember that the true roots of malnutrition ramify very deeply into the social and economic fabric of a society. In practice, all of the so-called causes are interrelated and interdependent: agriculture, climate, economics, cultural and social patterns, transportation, communication, education and even religion exercise influences.

Fundamentally, however, the main root of malnutrition lies in agriculture. The key to permanent correction of malnutrition lies with those measures necessary to increase agricultural production. Expansion of agricultural production is necessary not only to provide the increasing quantities of foodstuffs needed by growing and often ill-fed populations. It is also an indispensable element in general economic development, to provide raw materials for expanding domestic industries, and with many countries to provide the foreign exchange for industrial development.

At the moment, on a global basis, alleviation of malnutrition rests fundamentally on the outcome of a very delicately balanced race between rapidly expanding populations and expanding agriculture. As is well known, the world population is increasing rapidly, on the order of 100,000 additional people each day (13). In many cases the highest rates of population increases are in those countries that can least afford it. If food production rises more slowly than population, then food prices rise and people have more difficulty in obtaining an adequate diet. More food may have to be imported in preference to capital goods. Thus, overall development of the country is retarded.

On the other hand, when agricultural production begins to exceed the rate of population increase, food will be cheaper and more abundant. There may be feedstuffs available so that a country can afford more desirable but more expensive foods such as animal and dairy products. At the moment, few underdeveloped countries can afford the luxury of animal foods. Rather, they must depend on the direct consumption of products of the soil, and must concentrate on crops having the highest calorie yields per acre. Green and leafy vegetables, for example, are an important protective element in most diets, yet the calorie yield per acre is so low in comparison to the major staples that they are often not grown on an extensive scale. Throughout the underdeveloped world major reliance must be placed on one or more of the 5 major staples, that is, rice, wheat, maize, cassava and millets. When a population must depend on one of these for its principal source of food, nutrition problems are to be expected.

Typically, adults seem to survive quite well on even these predominantly cereal diets. It is the vulnerable groups—infants, pre-school children, pregnant and nursing

women—who have difficulty in obtaining the quantities of nutrients they need and it is in these groups that malnutrition first appears.

Economics obviously enters into this problem. With ordinary laborers earning 20–35 cents per day (U. S. cents), it is understandable that a man might have difficulty in providing for a wife and several children, even if rice costs only 5 cents a pound. All over the world there is a good inverse correlation between economic levels and nutritional problems. Yet so far as the individual and his family are concerned, purchasing power does not have quite the same significance as it does in our type of society. In most of the underdeveloped countries, 80% of the population is rural. Food to them is something you grow first of all to eat, although they sell some produce for other necessities of life, such as salt, sugar, beer, wives and bicycles. All too often the produce they sell is the meat, milk, eggs and vegetables which are short in their own diets.

It should also be noted that in this type of environment, increased cash purchasing power does not necessarily mean better nutrition immediately. Often the reverse is true, at least on a short-term basis. The Alaska Eskimo is perhaps a classic example. Their native diet is reasonably adequate. Yet, when jobs with cash income become available, they forget their native ways of procuring food and come to depend on what they can buy in stores. The food they buy tends to be the cheapest available, namely, highly refined white flour, sugar, carbonated and alcoholic beverages, not to mention radios, washing machines and similar items.

This same type of phenomenon is now appearing in many of the underdeveloped countries. All over the world there is a rapid migration to rapidly growing cities. People are attracted by seemingly good wages. However, they soon find that such wages won't go far when they have to purchase all of the food for their family. Often such families are worse off nutritionally than if they had remained in their rural environment. Rapid urbanization and industrialization are beginning to bring types of nutrition problems just as, historically, they have in most countries that have gone through industrial revolutions.

It is clear that in thinking of ways in which malnutrition can be corrected, the main problems, the main solution must lie in agriculture and the measures related to it. Yet, we know that agricultural improvements occur slowly. In the last 10 years, on a world basis, agricultural production has barely kept up with increasing population (14).

In view of the well-known population problem, one could wonder why I have not placed more stress on birth control as a means of insuring more adequate food. Unquestionably, this is important. Much attention is being given to it. However, I am rather pessimistic that this approach will have much impact in the immediate years ahead (15). To be realistic, one must rely on measures related to agricultural production and food consumption rather than on artificial methods which are so fraught with human frailty.

If one grants that agricultural improvement will be slow, one is then left with the question as to what can be done about malnutrition in the existing situation. This is the practical situation that confronts nutritionists. Malnutrition exists. We must deal with it in some fashion.

When one examines nutrition situations and problems in some detail, many additional causative factors and possibilities of improvement come to light. One encounters the food taboo, unsound food beliefs and practices. There are the groups who have eggs but won't eat them; the groups who believe that cow's milk is not a proper food for children. There are thousands of these unusual beliefs. There are social and economic conditions that contribute to nutrition problems. For instance, in Ruanda-Urundi there are thousands upon thousands of cattle which are not kept for their milk or for their flesh. They constitute the bank accounts of the native families and are a symbol of their wealth and social prestige. They would no more think of eating the flesh of one of these cows than we would of eating a $20 bill. Yet these cattle occupy much land that could otherwise be used to produce human food.

There is also much wastage of food in

these countries. This isn't 'plate waste' as we have it; it is waste in the field and waste in storage which often accounts for 10–30% of a crop.

In view of these facts, there are three main measures that nutritionists can take which offer hope of improving nutrition problems.

1) Nutritionists can and must participate in the formulation of long-range national development plans for agriculture, health, education, trade and economics. These are the so-called 'five-year or ten-year plans.' The nutritionist must see that these plans have a solid nutritional foundation and practical nutritional objectives. Oftentimes this is not the case. The main reason that nutritionists have not participated more in this type of planning is due to the training and experience of most nutritionists. Few of them have been trained to realize the decisive importance of economics, trade policy, the impacts of industrialization, urbanization and many other facets of development which at first seem remote from nutrition, but which actually are often decisive. Nutritionists must learn to take account of them and must learn to use such factors in programs of nutritional improvement.

2) The second general measure which the nutritionist can utilize is in the general field of education. Nutrition education, both by teaching and by practical demonstration, can be aimed at countering the food taboos, improving cooking and feeding practices, teaching mothers how to better feed their children with available food, promoting home gardens, home food production and preservation, as well as educating people in the basic elements of good nutrition. The fundamental aim here is to improve the utilization of existing resources. Education also is fundamental to long-range agricultural improvement.

3) The third main approach which a nutritionist can pursue is special measures to protect the most vulnerable segments of the population. In the main, this means the infant and the pre-school child, pregnant and nursing women. Special programs to provide protective foods to these vulnerable groups, combined with education and practical demonstration, can do much to alleviate malnutrition.

One might wonder why I have laid such heavy emphasis on the agricultural aspects rather than the health and medical aspects which actually are closer to my personal interest. I have done this deliberately because it seems to me that we as nutritionists have been too superficial in our approach; we have tackled symptoms rather than causes; we have neglected the obvious. We see the problems, which are obvious. We tend to attack the problem by the most direct route and with whatever means are at hand. This is human and natural. However, such efforts often are of only temporary benefit and at times I wonder if they may be harmful. We often try to correct food habits and beliefs that are obviously wrong to our minds, yet we forget that many of these countries have civilizations far, far older than our own. They have developed their beliefs and practices over centuries and, with them, they have survived and they have multiplied. I think at times we tend to change some of these patterns a little too rapidly, with too little and too superficial information.

The tragedy of malnutrition, of course, is that it is preventable if only we could apply the scientific knowledge we possess. This applies not only to malnutrition but in large measure to agriculture as well. The challenge to nutritionists is to find ways in which this knowledge can be applied, correcting the basic causes of malnutrition within the framework and within the possibilities which exist.

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World-Wide Occurrence of Protein Malnutrition

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IN 1933 Dr. Cicely Williams, working in the Gold Coast, colony of Western Africa, wrote (1):

"There is a well-marked syndrome... which I have not found described. (It) consists of oedema, chiefly of the hands and feet, followed by wasting; diarrhoea, irritability; sores, chiefly of the mucous membranes; and desquamation of areas of the skin in a manner and distribution which is constant and unique.

The disease attacks children of either sex, between one and four years old. It appears to be due to some dietetic deficiency and to be uniformly fatal unless treated early.

In all of the cases seen there was a history of an abnormal diet. Breast-feeding had been given by an old or else a pregnant woman, and the only supplementary food consisted of preparations of maize.

This defective feeding has gone on for four to twelve months. Then he (the child) begins to get irritable; there are attacks of diarrhoea; and swelling of the hands and feet. At the end of a week to ten days, the skin changes set in. If untreated, the child dies, generally within a month of the skin changes... The hair also... becomes dry, pale and sparse."

Her description of the skin changes is still unsurpassed:

"There suddenly appear on the ankles, on the knees, above the wrists, and on the elbows, some small black patches, first on the extensor surfaces and gradually spreading. .... The number and extent of these patches increase. Their distribution and their character remain distinct from the rash that is typical of pellagra. Soon the legs and forearms, knees and elbows, are covered with a sort of crazy pavement of this thickened epidermis. In a few days as the older patches mature, they strip off very readily, leaving a pink, raw surface exposed underneath. ... The patches of desquamation progress up the thigh and may become severe on the buttocks. Very small patches may also be seen on the face, back and elsewhere. The appearance of the skin condition at this stage is striking. There is the dark or reddish brown of the unaffected skin, the black patches of crumpled and thickened epidermis, and the raw areas where these have peeled off."

Three years and sixty cases later, Dr. Williams amplified her description of the disease and for the first time applied the local native name 'kwashiorkor' to it (2). This, of course, is neither the beginning nor the end of the kwashiorkor story. Although Dr. Williams did not know it at this time, she was merely giving one more name to a condition which had puzzled and disturbed many other persons and which was soon destined to become recognized as a major health problem in the world's technically underdeveloped areas.

Some of the descriptions in colonial times of the consequences of the artificial feeding of infants with cereal pap sound very much like the same condition (3). Nevertheless, as far as we can determine, the first clear description of the disease was published by Czerny and Keller in Germany in 1906 (4) under the name of 'Mehlnarschaden,' literally, 'starch dystrophy.' The syndrome seems to have been next recognized in Yucatan, Mexico in 1908 by Correa (5) as 'Culebrilla' which refers to the 'snake-like skin.' The disease was next described in Africa in 1918 by Jamot (6) who used the French West African name 'Dacaga,' and McConnel (7) in Uganda who called it 'edema disease.' During the 1920's reports were appearing with increasing frequency from almost every part of the globe. The disease was described in 1923 from Japan as 'Chichiko dyspepsia' (8); in 1924 from Kenya as 'edema with ascaris' (9); in 1927 from Italy as 'starch dystrophy' (10); Haiti as 'edema disease' (11) and France in 1927 (12) and Cuba in 1929 (13) as 'nutritional edema.'

Special mention should be made of the description of Normet (14) in Indochina who used the name 'Annam swelling' and wrote in 1926 that the evidence pointed to a disturbance of nitrogen metabolism. He not only considered the disease to be a new clinical entity, but also stated it to be the major cause of death in this country in adolescents and adults as well as young children. In 1928 Normet (15) again rejected completely the prevailing view that various infections and particularly hookworm could be responsible for the disease and reasserted it to be a manifestation of protein deficiency.

In South Africa the syndrome was called 'infantile scurvy' in the early 1930's (16) and 'infantile pellagra' throughout the 1940's (17). An account by Lieurade (18) in French Equatorial Africa, contemporaneous with that of Williams, referred to it as 'red children,' a name which mistakenly came to be considered by some later writers as the meaning of the word kwashiorkor. The literal translation of the 'Ga' word kwashiorkor is revealing of native insight into the epidemiology of the disease since it means 'first-second' and refers to the fact that the disease tends to occur in the first child when a second is born, i.e. when the first child is deprived of mother's milk (19).

Concurrent with and subsequent to the 1932 and 1935 reports of Williams, and generally without knowledge of them, the disease described by her as kwashiorkor was reported for the first time in many more countries—in 1934 in Tanganyika as 'Gillan's edema' (20) and in El Salvador as 'infantile edematous cachexia' (21); in 1937 as 'avitaminosis' in the Belgian Congo (22); in 1938 as 'vitamin deficiency edema' in Costa Rica (23) and as 'multiple dietary deficiency syndrome' in Guatemala (24). This name was also used in reports from Honduras (25) and Venezuela (26) in 1939. In the same year in Egypt (27) and Morocco (28) the name 'nutritional edema' was used.

And so the story continues—After 1940 recognizable descriptions of kwashiorkor added many additional countries, among them Chile (29), Colombia (30), China (31), Uruguay (32), Nigeria (33), Brazil (34), Rhodesia (35), Jamaica (36), Hungary (37), Greece (38), India (39), Indonesia (40), the Philippines (41), Fiji (42), Curaçao (43), Spain (44), Ceylon (45). The 1949 monograph by Meneghello (46) of Chile on *Multiple Deficiency Dystrophy* is still one of the most complete discussions of kwashiorkor available.

In 1950 an event occurred which was to tie these scattered studies together and guide the world's physicians and health workers to the cause and prevention of the syndrome, but other developments led to it. The Food and Agriculture Organization of the United Nations (FAO) was founded in 1945 and the World Health Organization (WHO) 3 years later. The first meeting of the Joint Expert Committee on Nutrition of the two organizations, held in Geneva in 1949 (47), had taken cognizance of ". . .The existence of a poorly defined nutritional syndrome of the tropics and subtropics, known by the name of Kwashiorkor, Malignant Malnutrition, Multiple Deficiency, Depigmentation-Edema Syndrome, Infantile Pellagra, etc. . . ."

The Committee recommended a study of the various aspects of kwashiorkor, and a commission made up of John Brock of Capetown representing WHO and Marcel Autret of FAO set out in mid-October of 1950 to visit the 10 countries and territories of Africa South of the Sahara. The result was the now famous Brock-Autret report (48) which firmly established the name kwashiorkor and which made it clear that the various other names referred to a single disease widely prevalent throughout Africa. The subsequent joint WHO/FAO surveys of Autret and Béhar (49) in Central America and Waterlow and Vergara (50) in Brazil made clear the essential identity of protein deficiency disease as it was widely occurring in Latin America with the kwashiorkor of Africa.

In 1953 WHO and FAO, this time with the assistance of the Josiah Macy Jr. Foundation, were once again responsible for a major stimulus in this field by arranging an international round-table conference of persons working with the syndrome, many of them without previous contact with similar workers elsewhere (51). Twenty-six persons from 12 countries and territories met in Jamaica for an entire week to discuss the problem of protein malnutrition and discovered, although a great deal of funda-

FIG. 1. Geographical distribution of kwashiorkor.

mental knowledge was still lacking, that they were unquestionably dealing with a common syndrome. Largely from the inspiration of this meeting and from a series of exchange visits among African, Indian and Latin American workers (financed by WHO) have come the numerous fundamental research studies of the last 5 years.

Progress was so rapid that when a second joint FAO/WHO/Macy Foundation conference was convened on the same subject in June 1955 in Princeton (52), emphasis was no longer on the clinical and biochemical characteristics of kwashiorkor or even its epidemiology, but almost entirely on how it could be prevented.

From this historical review it should be apparent that kwashiorkor is not a rare and exotic disease affecting a few children in a small number of far away tropical countries but, as figure 1 illustrates, is a major public health problem for a very large proportion of the areas and peoples of the world.

Thus far only the amount and distribution of clinical kwashiorkor have been mentioned, but frank cases of the syndrome are only a small part of the total problem of protein deficiency in children. They indicate a very widespread, frequently almost universal, occurrence of protein malnutrition in the general child population of pre-school age in an area. The prevalence of kwashiorkor has been compared with the visible portion of an iceberg which has six-sevenths of its bulk concealed beneath the surface of the water. Such a comparison, although graphic, fails to indicate the true quantitative relationship. For every case of kwashiorkor occurring in a population, there are not six, as suggested by the iceberg simile, but at least a hundred cases of underlying protein malnutrition—sometimes referred to as prekwashiorkor. The simile of the kwashiorkor-prekwashiorkor relationship should not be an iceberg but an underseas mountain with only the tip of its peak protruding above the surface.

Physicians working with children in hospital or outpatient clinics in areas in which kwashiorkor is endemic recognize severe protein malnutrition to be a serious problem. There is, however, a notable lack of appreciation of its magnitude and importance on the part of public health administrators and vital statisticians, who usually consider diarrheal disease a far more serious problem in this age group. Furthermore, the vital statistics gathered from these regions seem to confirm this latter point of view. The explanation lies in the fact that deaths of children with kwashiorkor are almost invariably listed as due to causes which are later coded within the category of diarrheal and parasitic diseases and hence are not identifiable in the official vital statistics of a country as deaths due to severe protein malnutrition. Furthermore, those deaths occurring in children with underlying protein malnutrition which are the immediate result of diarrheal and other infections are quite

TABLE 1. DEATHS 1–4 AGE GROUP 4 GUATEMALAN HIGHLAND VILLAGES

CAUSES	CIVIL REGISTER	INCAP STUDY
RESPIRATORY INFECTIONS	15	15
INFECTIOUS DISEASES	11	14
PARASITIC DISEASES	45	0
DIARRHEA	15	25
SEVERE MALNUTRITION (MOSTLY KWASHIORKOR)	1*	40
OTHER	22	15

* DIED IN A HOSPITAL INCAP-1958

naturally not listed as due to malnutrition, even though a well-nourished child would not have died from the infection alone.

These points are well illustrated by a recent 2-year study carried out in 4 representative villages in the Guatemalan highlands (53). Each death was personally investigated and the causes determined in this manner compared with those given in the Civil Register. With a single exception, the latter were based on the statements of the parents as interpreted by the town Secretary. The results are shown in table 1. Of the 109 child deaths 1–4 years of age investigated over a 2-year period, 40 occurred in children with the signs and symptoms of clinical kwashiorkor, yet only one was officially listed as dying from malnutrition and this was the only child in the group to die in a hospital and to have his death medically certified. The deaths of most of the children dying with kwashiorkor had been ascribed in the town records to 'parasites' or to 'worms.' Twenty-five children died of infectious diarrhea and an additional number of other infectious diseases which would not ordinarily have been fatal to a well-nourished child.

It is not exaggerating the role of protein malnutrition in this situation to point out that the difference between the mortality rate for children 1–4 in these villages of 42/1000 during the study compared with 1.1/1000 in the United States in 1956 could largely be eliminated if protein malnutrition could be prevented. Elimination of the infectious disease might also prevent the majority of these deaths, but it would not restore normal growth and development to children in this area.

The main characteristics of kwashiorkor are now familiar: retarded growth and development, apathy and anorexia, edema, pellagroid skin lesions, alterations in the color, texture or implantation of the hair, fatty liver, and diarrhea. Not every one, however, realizes that protein malnutrition is found in a continuous range from the classical forms in which calories are adequate, even abundant, as in the 'sugar-baby' type described from Jamaica (54), to those in which there has been a severe calorie deficit and considerable wasting has ensued.

In the sugar-baby type of kwashiorkor in which calories have been abundant and tissue wasting has not occurred, the child has all of the characteristic clinical, biochemical and pathological lesions of kwashiorkor, recovers readily when fed protein of good quality, and once the edema has disappeared, looks relatively healthy.

In a child with marasmus tissue wasting occurs as a result of partial starvation. Such a child has suffered protein deficiency but with an equally severe calorie deficiency, so that he has been to some extent living on his own tissues. For these reasons he does not develop the clinical, pathological or biochemical stigmata of kwashiorkor. The kwashiorkor syndrome as it is most often seen in nearly all endemic areas is combined with a varying degree of marasmus and is often spoken of as marasmic kwashiorkor.

The age at which weaning takes place and its abruptness largely determine the extent to which tissue wasting occurs before the signs of kwashiorkor are superimposed. In Latin America many cases are so close to marasmus that after treatment has been initiated and the edema has disappeared, they are indistinguishable from it except for the possible persistence of traces of the former skin lesions and of discolored bands in the hair. Clinical history can often be read in hair; in the simplest case an outer band of light brown corresponds to a period

of underlying protein malnutrition preceding the development of clinical kwashiorkor; a pale whitish band in the middle corresponds to the episode of kwashiorkor, and a black band at the base is normal hair growing out during treatment in the hospital. Depending upon the past history, additional bands may be seen.

Once the range of possible relationships between protein and calorie deficiency is understood and the different vitamin deficiencies which may be associated with kwashiorkor in various degrees are recognized, regional differences are easier to understand and it becomes clear that the basic syndrome is the same the world over. Most authorities working in the field now believe that the basic cause of kwashiorkor has been established conclusively to be a deficiency of protein relative to calories. It has been repeatedly demonstrated that the syndrome responds promptly and completely to skim milk or to vegetable mixtures of good protein quality (55). These preparations are, of course, also sources of other essential nutrients, but it has been further shown that the basic signs of kwashiorkor disappear or are greatly improved when vitamin-free casein (56) or even suitable mixtures of synthetic amino acids (57) are given.

That vitamin deficiencies become limiting and vitamins are required for further recovery beyond approximately 2 weeks, in no way weakens the argument for protein deficiency as the basic cause of kwashiorkor, since no animal organism will do well for any length of time on a diet providing protein, calories and minerals but no vitamins. The argument that kwashiorkor should be traced to the deficiency of one or more individual amino acids is not a very practical one. Even though certain of the signs of kwashiorkor may be due to deficiencies of specific amino acids, all of our growing knowledge of amino acid requirements suggests that the adequate utilization of any single essential amino acid requires that a balanced mixture of all be administered.

Kwashiorkor does occur in adults and has been so described from a variety of countries (58, 59). It occurs most often in pre-school children, however, because the diet after weaning is particularly likely to be relatively deficient in protein and because the protein requirements of the child per kilogram of body weight are higher at this time than at any later period in life. It is also an age when children are particularly vulnerable to the infections which precipitate kwashiorkor, since exposure is heavy and they have had little opportunity to build immunity.

The influence of infection on the development of kwashiorkor has been frequently recognized, but the extent to which it is an almost universal factor has only recently been appreciated. Infection reduces net nitrogen retention, due largely to increased nitrogen excretion in the urine, and is a direct precipitating factor in kwashiorkor. It also has an indirect effect, since in areas in which kwashiorkor occurs, the mother often treats the infection by withdrawing what little solid food the child may be getting and administering only thin cereal or starch gruels of negligible protein content. If the infection is enteric, as is very commonly the case, she may even administer a strong purgative to help get rid of the worms she believes to be responsible.

Even though there is no doubt as to the contribution of infection to mortality from protein deficiency, uncertainty remains as to the mechanism whereby protein deficiency increases mortality from infection. Although there may be little effect on resistance to initial infection, the capacity of the body to withstand the effects of infections and infestations and to resist secondary complications is reduced. This is an area in which additional clinical and epidemiological research is badly needed.

A discussion of world-wide protein malnutrition would not be complete without mention of general measures for its prevention. To help prevent deaths from kwashiorkor in endemic areas, professional and lay people alike should be taught to recognize the disease and to know that its true cause is the failure to consume foods which will supply protein of good quality. The application of modern knowledge to the prevention of infectious diseases for which effective immunization is available, and the improvement of environmental sanitation for the control of enteric disease will also reduce kwashiorkor. The primary goal of prevention, however, is not merely the elimination of kwashiorkor, but the restoration of normal

growth and development and good resistance to the complications of infection. This requires that adequate supplies of protein-containing foods be available at reasonable cost for the supplementary and mixed feeding of infants and young children.

Much is being done to increase milk production and conservation in technically underdeveloped areas and to make surplus skim milk available for relief purposes. Nevertheless, for many areas—for agricultural, economic or cultural reasons—there is no reasonable expectation of solving the problem with milk alone.

One important result of the recommendations of the 1955 Princeton conference (52) is that WHO and FAO, joined by UNICEF, have initiated intensive efforts to stimulate the production of protein-rich foods in areas in which kwashiorkor is endemic. The Rockefeller Foundation has also made funds available to the National Research Council to support research in this field. As a consequence progress is being made in many centers in the development of inexpensive and effective combinations of foods of vegetable origin of good protein content and quality. These centers include the University of Capetown in South Africa, the Institute for Scientific Research in the Belgian Congo, the University of Dakar in French West Africa, the Group for Research in Infantile Malnutrition in Uganda, the Health Department of Nigeria, the Central Food Technological Research Institute in Mysore and the Institute of Nutrition in Coonoor—both in India, the Children's Hospital in Mexico and the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala.

In the latter Institute several all-vegetable formulae have been developed with a protein quality comparable to that of milk. These have proved entirely satisfactory even as the sole protein source for the treatment of severe kwashiorkor. The latest of the formulae, INCAP Mixture 9B, contains only corn, sorghum, cottonseed meal, yeast and added synthetic vitamin A, yet provides all of the requirements of a child at weaning, except for calories and vitamin C, for an ingredient cost of 2 or 3 cents a day. On such vegetable mixtures and the increased availability of milk, fish and other animal protein sources, together with intensive educational efforts, rest the hopes for eliminating kwashiorkor and the underlying protein malnutrition which precedes it and which contributes to mortality from infections.

The objective of the many national and international efforts to achieve this goal is to ensure that the ordinary children in the areas in which kwashiorkor is endemic, whose growth and development are now retarded, whose resistance to the consequences of disease is lowered and whose vitality is sapped by protein malnutrition, are converted into healthy youngsters. Only then can they be expected to absorb the knowledge and learn the skills and attitudes required to build a stable, prosperous and peaceful world.

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Progress in Understanding and Preventing Protein Malnutrition in Central America

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SEVERAL OF THE CONCEPTS expressed in this paper represent the opinion of Dr. José Maria Bengoa, from the Nutrition Section of WHO, or constitute the results of work carried out in Central America by Dr. Nevin Scrimshaw and Moises Béhar from the PASB/INCAP Staff.

As in most other technically underdeveloped areas, protein malnutrition is prevalent among the rural and semiurban population of the Central American countries.

The manifestations of this deficiency cover a wide spectrum of clinical signs and symptoms, and occur especially among pre-school children who constitute the population group most severely attacked. Some of these manifestations are conspicuous and frequent: *1*) Physical development is retarded and growth and maturation practically stop during the second and third years of life. In Central America it is difficult to see the difference between a 2- and a 4-year-old child in the rural and poor urban areas. *2*) Physical signs, such as easily detachable hair, mucous membrane lesions and pretibial edema occur frequently. *3*) A large number of hospital children with kwashiorkor or marasmus are seen in the pediatric wards all through the area. *4*) Children from 1 through 4 years of age die with an alarming frequency. The mortality among children of this age is generally accepted by Public Health authorities as a good index of the problem of protein malnutrition. The overall rate of this mortality for 1956 for Central America was 26 per thousand (data from Dept. of Statistics, Central American Countries) which, when compared with a rate of 1.1 for the United States (1) gives an idea of the severity of the problem.

Dr. Scrimshaw has reviewed the epidemiology of protein malnutrition on a world-wide basis. The situation in the Central America area may be considered representative. Studies have been conducted in order to understand how causative factors operate in the production of this deficiency. From such studies, we can picture the life of a typical child from the time of gestation to 3 or 4 years of age as follows.

In a poor home, usually a hut, lives a woman who does not know how to read or write; the mother of 2 children, ages 2 and 4, who is now in the sixth month of pregnancy. This mother looks thin and is not gaining the weight she is supposed to gain during pregnancy. She lives alone since her last husband, who spent most of his earnings on alcohol, has abandoned her. She cannot afford to eat better because her earning as a laundress amount to only 50 cents per day. Three months later, in the midst of this poverty, adverse social conditions and ignorance, a baby is born and, strangely enough, his birth weight is normal—about 7 pounds. The baby is breast-fed and, during the following 6–8 months, he maintains a satisfactory nutritional status and grows relatively well. By the age of 6–8 months, the mother's milk starts to be insufficient for the baby's requirements and as a consequence, growth and maturation begin to slow down. After one year, tortillas (corn meal), the cooking water from beans, coffee and occasionally fruits and vegetables are given in addition to breast milk. In children such as these, weaning occurs sometime between 1 and 3 years. Unfortunately, the same type of diet is continued and, consequently, growth and maturation practically stop.

The three main reasons for the existence of such poor child feeding practices are: first,

erroneous beliefs, such as harmful effects of some foods; second, ignorance concerning the need for a good diet and the way of preparing it; and third, a low family budget. However, in most instances the mother with a limited budget would be able to feed her child in a satisfactory way if only she knew how. At any time during this period, as the result of the environmental conditions in which the child lives, enteric infections and attacks of diarrhea make their appearance; the diarrhea is believed by the mother to be due to intestinal parasites and is treated by means of an even more restricted diet and by the administration of laxatives which only aggravate the nutritional status of the already malnourished child. A few weeks later the signs of kwashiorkor are present. If lactation fails during the first 6–9 months of life, marasmus is more likely to appear.

In some cases, it is during the convalescence from an infectious disease, such as measles, that severe malnutrition appears. Ignorance comes again into play. Due to the fear of 'damage to the kidneys' said to be produced by meat, milk or heavy food during this delicate state, watery diets are imposed for several weeks. The stress of an inadequate diet is added to the stress due to measles; kwashiorkor or marasmus will be the result. Ignorance is at this stage the main precipitating cause of severe malnutrition.

In summary the predisposing factors of poverty, adverse social conditions and a low educational level are generally present (fig. 1). The critical period begins at 6 months and lasts 3–4 years. Infectious diseases, lack of good-quality foods and, especially, ignorance of the mother are the factors that precipitate malnutrition. Let us now consider what we are doing in the field of prevention.

PREVENTION

From a long-range point of view the control of the predisposing factors of malnutrition is essential for a permanent solution of the problem. Only permanent improvement in educational, agricultural, economic and sanitary standards of living will ultimately bring about a lasting solution.

The process of educating towards better health habits, particularly creating the desire to adopt new dietary practices, is intimately related to teaching how to grow more and better food and how to prepare it. In the overall nutrition program, the task of Public Health workers is that of teaching health and nutrition practices to mothers of children attending the Health Centers; the task of agricultural extensionists is teaching how to grow better food in the school and family gardens; and that of school-teachers is the giving of instructions in health and nutrition through school programs. These activities are intimately interdependent and in order to be fully effective should be carried out simultaneously. INCAP is working with

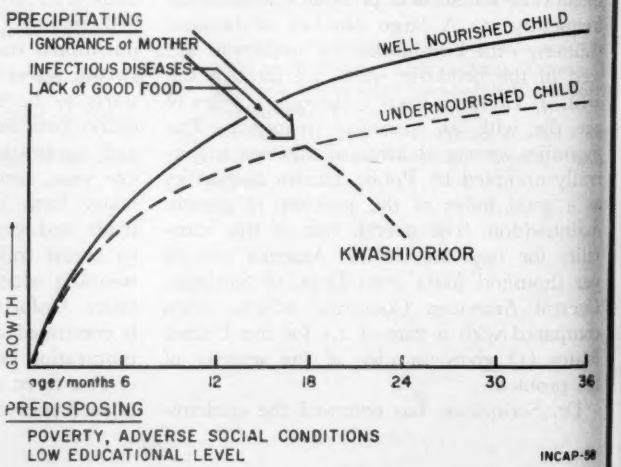

FIG. 1. Factors in production of protein malnutrition in Central America.

the National Public Health, Education and Agriculture Departments of its member countries to help bring this about.

There are, however, emergency measures which are also required. The Central American countries are facing now a critical problem posed by the thousands of children who are dying each year and for whom something should be done at once. This immediate action towards the control of disease and death is being taken along the following lines: *a*) against the ignorance of the mother: nutrition education; *b*) against infectious diseases: environmental sanitation; *c*) against the lack of good food: availability of inexpensive foods of high nutritive value such as vegetable mixtures.

Let us now consider one of the most important of these actions.

Nutrition education. In Central America there is an urgent need not only to take care of the child before weaning but also to extend this care to the postweaning period. This problem is being increasingly recognized by personnel of the local health services, and programs have been initiated to educate the mother as to the best way of gradually introducing the child into the complete family diet.

In one sense, severe protein malnutrition in children is a 'deficiency' of the mothers and they can be said to be the ones requiring the 'treatment.' Health Services are being used to 'treat' the mothers with education in the better care of their children. This education is centered around three main points. First, the mothers are encouraged to pay attention to the weight of the child and to recognize it as an index of his nutrition and good health. Second, the importance of a good diet for the maintenance of health and adequate progression in weight is emphasized; and finally, the mothers must be convinced of how harmful some of their beliefs are and how important it is for them to make the necessary changes. Action programs based on these three points are the responsibility of all Health Center personnel, although a special burden falls on the Public Health Nurses.

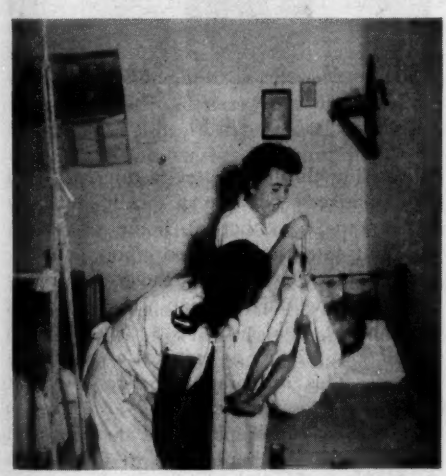

FIG. 2

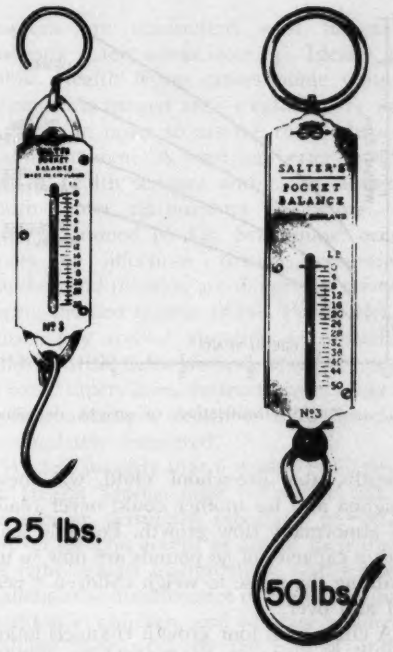

FIG. 3. Scales in use by Public Health nurses in Central America.

Interest in body weight is aroused by the nurse who, equipped with portable scales and charts, tries to obtain the active participation of the mother in the weighing of the child (fig. 2).

Public Health Nurses were until recently equipped with scales of only 25-pound capacity (fig. 3); with these, they could weigh only children below 1½ years of age. Conse-

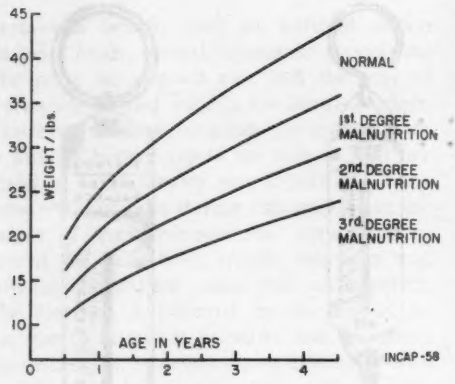

FIG. 4. Rapid classification of weight deficiency.

FIG. 5

FIG. 6

quently, the pre-school child was never weighed and his mother could never realize his abnormally slow growth. Portable scales with a capacity of 50 pounds are now in use, enabling the nurse to weigh children 5 years old and over.

A chart with four growth channels following a scheme proposed by Gómez and coworkers (2) is a guide to the nurse for the rapid classification of the severity of the weight deficiency (fig. 4). Children who fall in *channel 1* are within ±10% of the average weight for well-nourished children. Children with 11–25% deficit fall within *channel 2*. A child with a weight within *channel 3* has a weight deficit in the magnitude of 26–40% and below *channel 3* are those children with more than 40% deficit in their weight. Most of these are cases of marasmus or kwashiorkor.

The nurse, in the presence of the mother, plots the child's weight on this chart and is now in a better position to explain to the mother the significance of the child's actual weight. The mother is in this way made aware of the significance of this measure of her baby's health. If the child is found to have a normal weight, the mother is congratulated and stimulated to keep her child in good health by continuing to feed him adequately. The nurse encourages her to continue good dietary practices and shows her how to prepare the baby's food. Children found underweight but not severely malnourished, *channels 2* and *3*, receive special attention. The significance of their low weight is explained to the mother and the need for rehabilitation through better feeding practices is emphasized. The use of locally available foods prepared either at home or at the Health Center is depended upon.

The objectives are to teach the mother through active participation and observation that all the child needs is a diet that she, herself, can prepare at home at no extra cost (fig. 5). This rehabilitation takes place at home or at the Health Center according to the type of community and the size and proximity of the population to the Health Center (fig. 6). If at all possible, children are taken to the Center by their mothers,

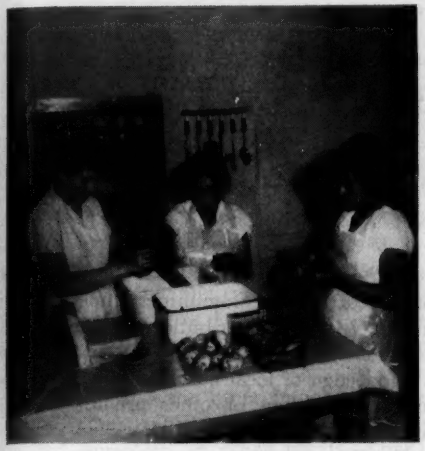

FIG. 7

who participate actively in the selection and preparation of food under the supervision of a Public Health Nurse (fig. 7). As mentioned previously, these so-called 'Rehabilitation Centers' also serve as training centers in Nutrition and Dietetics for Public Health Nurses.

Children falling in the fourth channel, with more than a 40% deficit in weight, are generally found to have either kwashiorkor or marasmus and require hospitalization. In this case, emphasis is placed on the education of the mother. She is taught that kwashiorkor and marasmus are manifestations of hunger, and that the child recovers by eating. In the past this was practically never done in hospitals in the area. Children with severe malnutrition were, and unfortunately in most cases still are treated and discharged without the mother ever learning about the nature of the sickness of her child and its cause. This type of hospital care treats the manifestations of the disease but ignores its real cause, the mother's own ignorance of proper feeding practices or misguided notions of therapy. This has been the reason why, in some areas of Central America, up to 50% of children treated and discharged from hospitals are readmitted with the same syndrome a few weeks later (3). Ideally, the Public Health Nurse makes home visits to children discharged after treatment for malnutrition in order to assume their adequate feeding at home. A need for better integration of health services and closer hospital-health center relationships is obvious.

As mentioned by Dr. Scrimshaw, occurrences of infectious diseases, especially diarrhea and measles, are dangerous episodes during the first 5 years of life. Public Health Nurses pay special attention to pre-school children with these diseases and, by means of close supervision, instruct the mother as to their adequate treatment until the child is completely recovered.

We feel strongly that nutrition activities in the Health Service must be carried out by the regular personnel, especially physicians and nurses who accept as one of their duties the fight against malnutrition, who see as a challenge the maintenance of health and good nutrition in children, and who are willing to evaluate their work by the rate of underweight, of kwashiorkor and of deaths in the children up to 4 years of age of the community under their care.

If the fight against malnutrition is to succeed, immediate action is essential in the reorganization and strengthening of health services, and the provision of adequately trained personnel in nutrition, namely nutritionists, for supervisory work of the regular Public Health staff. The Institute of Nutrition of Central America and Panama (INCAP) will continue working in close cooperation with other agencies towards improving the nutritional status of the populations of Central America and Panama. INCAP has completed plans for a 4-year university level School of Nutrition and Dietetics to help meet the problem of an almost complete lack of nutritionists and dietitians in Northern Latin America. It is also accelerating its training of physicians in Public Health Nutrition.

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Summary

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IT IS NOW MY DUTY to attempt to summarize for you what the speakers have so ably told us about a problem that is of tremendous world-wide importance. It is perhaps the solution of this problem alone that should occupy much of the time and thoughts of any group who are planning, in any country, for the next 20 or 30 years. The speakers have first emphasized the importance of the assessment of the problem in any given area, namely, the determination of where, to what extent and to what degree malnutrition exists.

Dr. Hundley pointed out the dangers of drawing too many conclusions from vital statistics collected in countries and I think it might be fair to say that the vital statistics of any country are just about as good as the nutrition in that country. We have too frequently used neonatal mortality as an index of the nutrition of a population. It is a crude index but if, as Dr. Scrimshaw noted, we could have more detailed information on the nutrition of the 1–4 year age group, which is particularly vulnerable, then perhaps we could get a better picture of what, in fact, was happening to the nutritional state of the population as a whole. The rapid growth of this age group and their inability to fend for themselves, make them the victims of the syndrome kwashiorkor, but they are relatively inaccessible because they are not at school.

The direct method of assessment, by the nutritional survey team, has, as Dr. Perez mentioned, become very much a science and technique of its own, meriting a university degree, and only where such surveys have been conducted for some time and on a large scale will we get the valuable information which we must have before the problem of correction can be tackled.

The survey team, apart from their clinical assessment of the population, must also get accurate data on the methods of cultivation practiced in the communities, the preparation, storage and distribution of food and, in addition, we have heard stressed the need for a knowledge of local customs and the possibility of religious or other prejudices controlling the use or lack of use of certain foodstuffs.

Malnutrition, itself, is a very widespread and comprehensive syndrome and it may result from lack of calories, protein, minerals or vitamins individually or collectively, and Dr. Scrimshaw has given us a very graphic description of the most important single problem that we face today—protein malnutrition which produces the syndrome kwashiorkor which has now been accepted as presenting a fairly uniform clinical picture throughout the world. I can well remember as recently as 1953 at an international meeting on malnutrition held in Jamaica, the discussions and the days it took before any kind of agreement could be reached and it is now most gratifying to see workers from Africa, from Indonesia, from India and from America agreeing freely as to what kwashiorkor is.

It is interesting that the name should have come to stay. It is the most difficult name of all that were coined, and perhaps that is why, in man's perversity, it has stuck!

The second and most practical aspect of this problem which was stressed was correction and the fundamental emphasis was rightly put upon the improvement of agriculture, particularly agricultural methods. Soil conservation, irrigation, fertilization and rotation of crops are what the agricultural officers must push in areas with such personnel, and Dr. Hundley pointed out that the only solution to this problem is to increase local production, both in quantity and quality, and that any measures which

mean importation into an area can only and must only be temporary measures.

The magnificent job of work which has been done by UNICEF in the distribution of skim milk, in the areas where this disorder exists, mustn't lull us into a false sense of security and we must push ahead with patience and persistence in the education of the community, first on an agricultural basis and, secondly, as Dr. Perez so ably emphasized, the education of the mother in the nutrition and the care of her child. Nutrition education as well as data collection must be an important function of the nutritionist and the survey worker.

There is also the other important aspect of education, and that is educating the educators—ourselves, in other words. That, I think, can best be achieved by exactly what has been happening over the last 6 or 7 years where the international organizations and some foundations, such as the Macy Foundation, through their generosity, have made it possible for all the workers in this field to meet fairly frequently, to argue the case and to come to agreement or agree to disagree. So long as we keep our ideas as dynamic as protein metabolism itself, we will continue to educate ourselves and educate the people in the field.

This need for open-mindedness applies even to something as fundamental as protein requirements. These, as you know, are still tentative. They are by no means agreed by all authorities, and although FAO published an able review of the present position, the members of the committee responsible would be the first to admit that it was no more than a majority report or a compromise. There may well be a warning in Dr. György's information that in certain species of rat, a low-protein diet which is isocaloric produces an increase in the life span by a year—which is an enormous amount in the rat—and reduces their susceptibility to infection. That should be kept in the background, but it emphasises the need for caution in laying down standards for general application.

It is also important that clinicians and other workers in this field should be on the lookout for a relationship between malnutrition in infancy and the development of disease in later life. We have heard a lot about degenerative arterial disease and overnutrition but undernutrition may also have its sinister sequelae. We have cirrhosis of the liver as a major problem in certain areas of the world where malnutrition is rife and where there is cirrhosis there is primary cancer of the liver. These relationships may be of fundamental importance in casting light on some of the unknown aspects of these problems.

Dr. Hundley mentioned population control. Unwillingly, I have to agree with him that, although on a long-term basis it must be the objective, it cannot be an immediate solution to the problem of the rapid growth of world populations. We must continue to make every effort to provide for it universally but it can never be more than a small part of better education in its widest sense.

BASIC RESEARCH

Introduction

FLOYD S. DAFT

National Institute of Arthritis and Metabolic Diseases

YESTERDAY a very penetrating look was taken at nutritional problems during the growing process and during middle age. This morning we have heard extremely interesting presentations on some world-wide nutritional problems. Now we come to the very important subject of basic research.

In the time at our disposal this morning it would obviously be impossible to cover the full field of basic research in nutrition. We are fortunate, however, in the choice of speakers to represent investigators engaged in basic research. Our first speaker is met all too infrequently, I am afraid, in nutrition meetings, although his contributions to the science have been very, very important. Dr. H. O. L. Fischer, now Chairman Emeritus of the Department of Biochemistry at the University of California, has had a distinguished career in Germany, in Switzerland, in Canada and in the United States. His contributions have been in the field of carbohydrate chemistry but without them biochemists would have found it impossible to advance as rapidly as they have in their understanding of enzymatic degradations of carbohydrates.

Our second speaker, Dr. Alfred E. Harper, Associate Professor of Biochemistry at the University of Wisconsin, has been engaged in the very important work of determining protein requirements and of translating them to more exact amino acid requirements. As we pass from protein to amino acid studies, there is danger of oversimplification and a belief that a few experiments will determine accurately the absolute requirements of these dietary components. Dr. Harper is doing us all a great service in emphasizing in his studies and in his presentation today the great importance of variables in relation to the determination of amino acid needs.

Frontiers of Research on Sugar

HERMANN O. L. FISCHER

University of California, Berkeley

IT IS ALWAYS with some kind of hesitation that I address a meeting on nutrition because my knowledge of nutrition is almost nil; but I am an organic chemist and Dr. Daft has already so ably explained and justified my presence here that I don't need to add anything more.

I am going to talk to you about two fields of organic chemistry, or biochemistry if you like, which have provided powerful tools of research in biochemistry and nutrition. You know there are many cases where analytical methods and procedures of isolation do not succeed because the 'key' substances are present only in minute quantities or so extremely sensitive as to be decomposed during the process of isolation.

Our laboratory has synthesized some of these compounds and my main examples in the 30 minutes I have will be the synthesis of triose phosphates and a tetrose phosphate. These are phosphate compounds of small sugars, 3-carbon atoms and 4-carbon atoms. Later I shall discuss a very different new field, namely, the synthesis of 3-amino sugars which now comes somewhat into the foreground in the chemistry of antibiotics and in other biological fields.

However, before I discuss these recent 'frontier developments,' I want you to look back for a moment into the past of sugar chemistry. Figure 1 shows the past master of carbohydrate chemistry, Emil Fischer, in his laboratory in Berlin about 60 years ago at the height of his career. At this time the configurations of glucose, fructose and mannose were still new and exciting and it is surprising that in these very much changing times of ours they are still true and important.

We have his Library in Berkeley, in the Biochemistry and Virus Laboratory, and also about 9000 of his reference compounds in the different fields he worked on, particularly carbohydrates, in the basement of our institute, and we have last but not least his laboratory stool. When we are stuck in our work, which is very frequently the case, and need some inspiration, we sit down on it and get it—from below.

Now I am earnestly coming to my proper subject. You see in figure 2 the well-known Embden-Meyerhof scheme of fermentation and glycolysis. Here the synthetic efforts of our laboratory have brought about the preparation of important intermediates. Seven of them were synthesized in pure form; their names are underlined on the figure. These compounds in the hands of Meyerhof and Embden have greatly helped in the development of the scheme. When I was in Basel, Switzerland, Meyerhof was in Heidelberg and Embden in Frankfort, so we frequently interchanged ideas, and I sent preparations over to help the biochemists.

FIG. 1

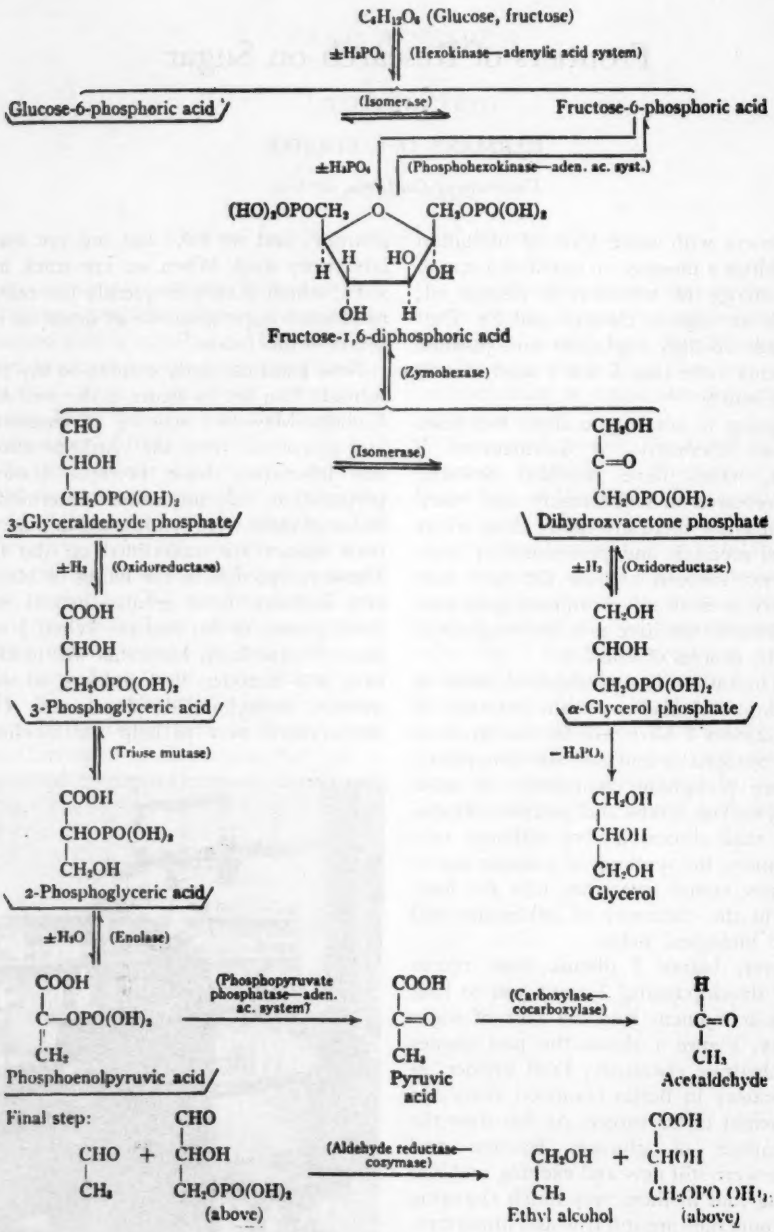
$C_6H_{12}O_6$ (Glucose, fructose)
$\pm H_3PO_4$
(Hexokinase—adenylic acid system)
Glucose-6-phosphoric acid
(Isomerase)
Fructose-6-phosphoric acid
$\pm H_3PO_4$
(Phosphohexokinase—aden. ac. syst.)
$(HO)_2OPOCH_2$
$CH_2OPO(OH)_2$
Fructose-1,6-diphosphoric acid
(Zymohexase)
CHO
CHOH
$CH_2OPO(OH)_2$
3-Glyceraldehyde phosphate
(Isomerase)
CH_2OH
C=O
$CH_2OPO(OH)_2$
Dihydroxyacetone phosphate
$\pm H_2$
(Oxidoreductase)
COOH
CHOH
$CH_2OPO(OH)_2$
3-Phosphoglyceric acid
(Triose mutase)
COOH
$CHOPO(OH)_2$
CH_2OH
2-Phosphoglyceric acid
$\pm H_2O$
(Enolase)
COOH
$C—OPO(OH)_2$
CH_2
Phosphoenolpyruvic acid
(Phosphopyruvate phosphatase—aden. ac. system)
COOH
C=O
CH_3
Pyruvic acid
(Carboxylase—cocarboxylase)
H
C=O
CH_3
Acetaldehyde
$\pm H_2$
(Oxidoreductase)
CH_2OH
CHOH
$CH_2OPO(OH)_2$
α-Glycerol phosphate
$-H_3PO_4$
CH_2OH
CHOH
CH_2OH
Glycerol
Final step:
CHO
CH_3
+
CHO
CHOH
$CH_2OPO(OH)_2$
(above)
(Aldehyde reductase—cozymase)
CH_2OH
CH_3
Ethyl alcohol
+
COOH
CHOH
$CH_2OPO(OH)_2$
(above)

FIG. 2

Of course, this scheme is now one of the best-established ways of sugar utilization both in the animal body and in alcoholic fermentation by yeast. I can bring you only a small part of this work and will describe to you only the synthesis of the two triose phosphates, namely, D-glyceraldehyde-3-phosphate and dihydroxy-acetone-phosphate.

The fermentation scheme of Neuberg didn't contain any phosphate at all for the very simple reason that triose phosphates, the D-glyceraldehyde-3-phosphate and dihydroxy-acetone-phosphate decompose under very mild conditions into inorganic phosphate and methyl-glyoxal, and this is the reason why methyl-glyoxal for some time was considered to be an intermediate of the fermentation scheme of Neuberg. Of course, these are past times now.

Now comes the synthesis of D-glyceraldehyde-3-phosphate which has been carried out with Dr. C. E. Ballou (1) in the Biochemistry Department of the University of California in Berkeley (fig. 3). One of our main difficulties was that the desired compound contains one asymmetric carbon atom. These compounds are much too sensitive to attempt any kind of optical resolution. So we had to start from optically active material. This is mannitol (I) which was condensed with two molecules of formaldehyde to form compound II. In II only the hydroxyl groups in positions 2 and 5 are free and can be benzylated in the usual manner forming III. By acetolysis, the formaldehyde groups in III can be eliminated yielding a 2,5-dibenzyl mannitol IV. This 2,5-dibenzyl mannitol can be split with sodium periodate between carbon atoms 3 and 4 into 2 moles of 2-benzyl-D-glyceraldehyde V. Compound V is the real key substance of the synthesis and can be transformed by five more steps into the desired D-glyceraldehyde-3-phosphate X. The steps are easily understood from the above scheme.

The synthesis of the other triose phosphate, the dihydroxy-acetone-phosphate, is somewhat simpler because the compound does not have an asymmetric carbon atom. We start from chlorohydrine and go through a series of steps indicated in figure 4. They are self-explanatory, so I will not bother you with the details which are described by C. E. Ballou and H. O. L. Fischer (2).

These are the syntheses of the two triose phosphates which did so much for the development of the fermentation scheme of Embden and Meyerhof, and here is a little

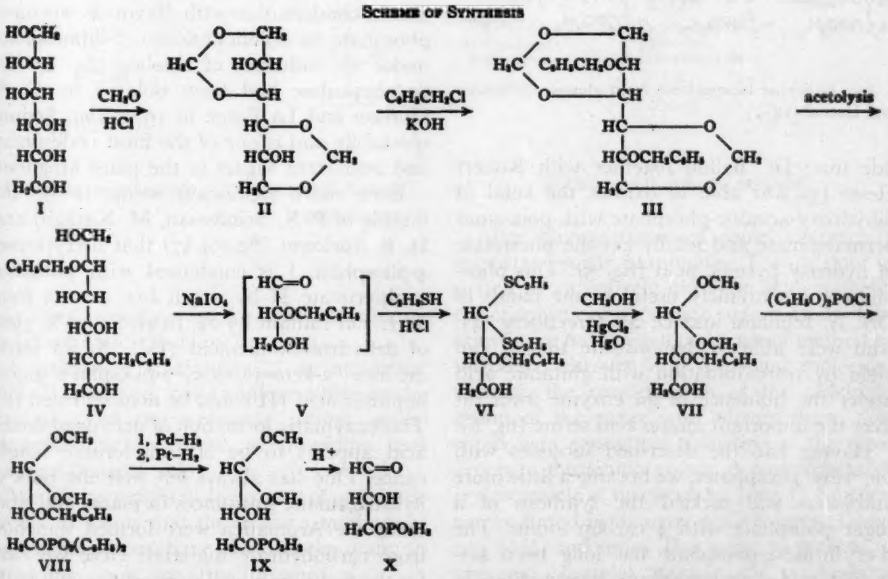

Fig. 3

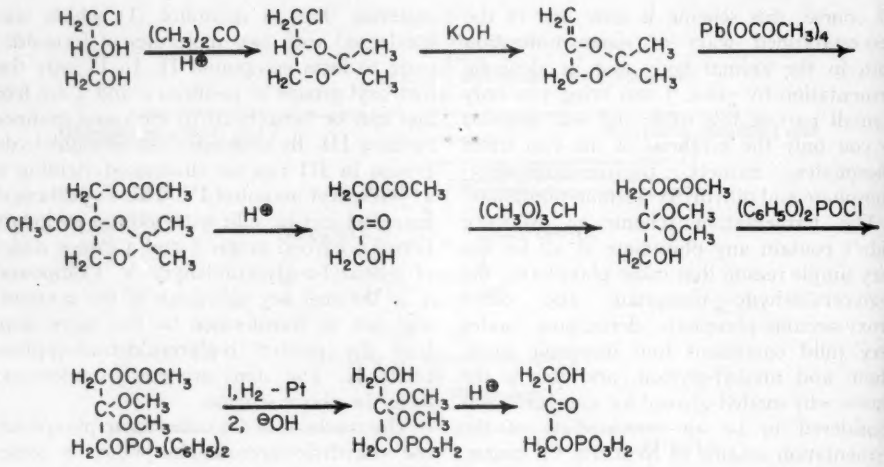

FIG. 4

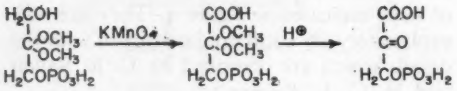

FIG. 5

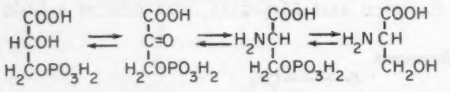

FIG. 6. Serine biosynthesis from glucose (Ichihara and Greenberg).

side line: Dr. Ballou together with Robert Hesse (3) was able to oxidize the ketal of dihydroxy-acetone-phosphate with potassium permanganate and finally got the phosphate of hydroxy pyruvic acid (fig. 5). This phosphate was extremely useful in the hands of Drs. A. Ichihara and D. M. Greenberg (4), who were able to demonstrate that it can yield by transamination with glutamic acid under the influence of an enzyme from rat liver the important amino acid serine (fig. 6).

Having had the described successes with the triose phosphates, we became a little more ambitious and tackled the synthesis of a sugar phosphate with 4 carbon atoms. The D-erythrose-4-phosphate has long been suspected to be an important intermediate in various processes in plant and animal metabolism, but it never has been isolated because of its sensitivity probably forming very easily furane derivatives.

We used very similar methods to those found useful in the chemistry of the triose phosphates. The scheme in figure 7 from Ballou *et al.* (5) is self-explanatory.

The synthetic D-erythrose-4-phosphate gives in good yield B. L. Horecker's well-known condensation with dihydroxy-acetone-phosphate to sedoheptulose-1,7-diphosphate under the influence of aldolase (fig. 8) (6). Sedoheptulose had been isolated by C. S. Hudson and La Forge in 1917 from Sedum spectabile and is one of the most widespread and important sugars in the plant kingdom.

Even more significant seems to be the finding of P. R. Srinivasan, M. Katagiri and D. B. Sprinson (fig. 9) (7) that D-erythrose-4-phosphate I is condensed with phosphoenolpyruvate II by a cell free extract from an *E. coli* mutant 83-24, to give a 90% yield of dehydroshikimic-acid (IV). As an intermediate 2-keto-3-desoxy-7-phospho-D-glucoheptonic acid III could be demonstrated (8). This enzymatic formation of dehydroshikimic acid appears to be of considerable significance. One has always felt that the bulk of hydroaromatic substances in plants and from them the Aromatica were formed somehow from carbohydrate material. Here we have for the first time a well-defined enzymic path-

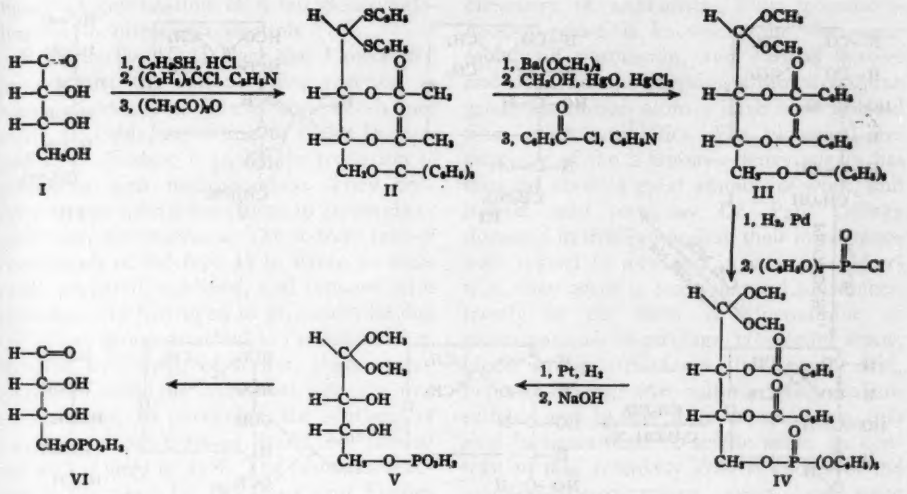

FIG. 7

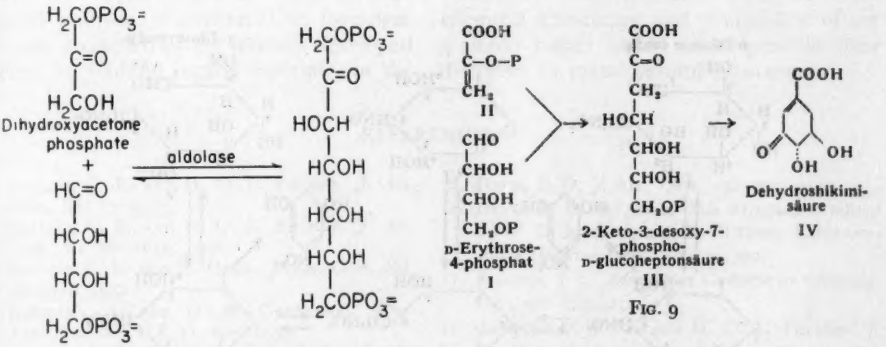

FIG. 9

way from phosphorylated carbohydrates to a hydroaromatic substance.

Furthermore shikimic acid is, according to B. D. Davis (9, 10) an intermediate in the formation of the aromatic amino acids: phenylalanine, tyrosine, tryptophane and *p*-amino-benzoic acid.

We are here right in the center of metabolic events. It seems that the modern methods of organic synthesis have done their share in providing tools for this progress.

NITRO- AND AMINO SUGARS

After having discussed some biologically important sugar phosphates, I want now to switch to an entirely different field, namely, the chemistry of the amino sugars. In my laboratory we have developed a novel method to introduce nitrogen into the sugar molecule, namely, the condensation of the aldehydo group of the sugar with nitromethane and subsequent catalytical reduction of the nitro group to the amino group. A comprehensive review article of this work by John C. Sowden can be found in *Advances in Carbohydrate Chemistry* (11), and today I'm going to present to you two examples, namely, the synthesis of

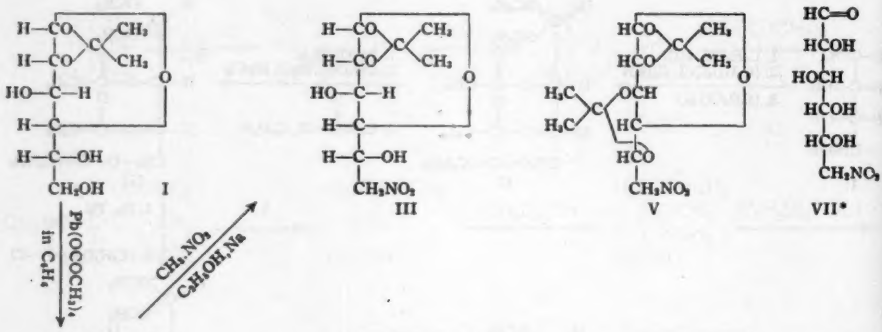

FIG. 10

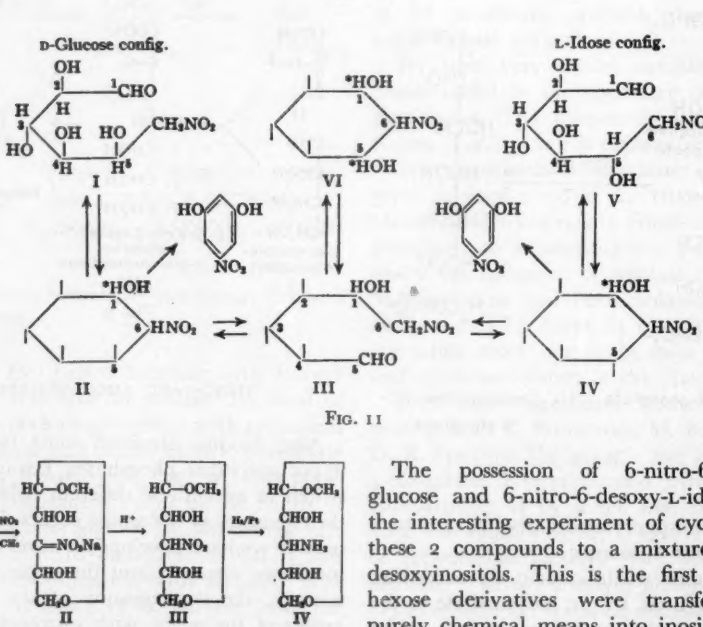

FIG. 11

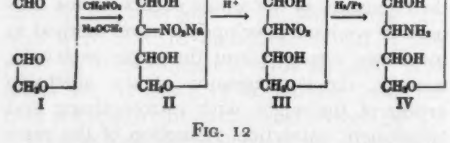

FIG. 12

6-nitro-6-desoxy-D-glucose and 6-nitro-6-desoxy-L-idose by J. M. Grosheintz and H. O. L. Fischer (12). The sequence of reactions leading to those compounds is well illustrated by figure 10.

The possession of 6-nitro-6-desoxy-D-glucose and 6-nitro-6-desoxy-L-idose led to the interesting experiment of cyclization of these 2 compounds to a mixture of nitrodesoxyinositols. This is the first time that hexose derivatives were transformed by purely chemical means into inositol derivatives. Of course, the nitrodesoxyinositols which we have prepared this way could easily be reduced to the corresponding amino compounds which have significance for the chemistry of streptomycin. The course of this reaction is again illustrated by

figure 11 (cyclization of 6-nitrodesoxyaldohexoses to nitrodesoxyinositols (13).

Recently Dr. H. H. Baer and I succeeded in applying the nitromethane reaction to sugar dialdehydes. These compounds are easily available, according to E. L. Jackson and C. S. Hudson (14), by the oxidation of glycosides with metaperiodate. They condense under special conditions in an excellent yield with nitromethane. The sodium salts of compounds of the type II in figure 12 were easily prepared, acidified, and reduced with platinum and hydrogen to glycosides having the amino group attached to carbon atom 3. By acid hydrolysis, of course, these amino glycosides could be converted into the free amino sugar. In particular, the synthesis of 3-amino-3-deoxy-D-ribose could be carried out with a yield of 35%. The course of reaction is described by Drs. Baer and Fischer (15) under the title, *A New Way for the Synthesis of 3-Amino Sugars.*

The wide applicability of the newly discovered pathway is obvious. Our investigation was prompted by the recently developed interest in 3-amino sugars, especially in the chemistry of antibiotics. Thus 3-amino-3-deoxy-D-ribose is known to be the sugar moiety of puromycin, and various hexoses and deoxyhexoses carrying a dimethylamino group on carbon atom 3 have been isolated from other antibiotics. The biological importance of the 2-amino-2-deoxy sugars has brought about a great amount of work, and indeed only yesterday Dr. György discussed in this Symposium their importance with regard to nutrition in infancy. Otherwise, they occur in many natural substances; mostly in the form of glucosamine or galactosamine, in cartilage, connective tissue, blood group substances, hyaluronic acid, heparin, chondroitin sulfuric acid, keratosulfate, and in the form of mannosaminic acid in neuraminic or scialic acids. In contrast to this, relatively little is known of the 3-amino-3-deoxy sugars, apart from some older investigation and the recent extensive studies of B. R. Baker and R. E. Schaub. I wouldn't be surprised, however, if the better chemical knowledge and availability of the 3-amino sugars would make possible their discovery in many natural substances.

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Advances in Our Knowledge of Protein and Amino Acid Requirements

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THE LOGICAL PLACE to begin a discussion of amino acid and protein requirements is with the discovery of threonine by McCoy, Meyer and Rose, in 1935 (1). And while I was thumbing through literature which I thought might be pertinent, I found reprinted in the Heinz and Company *Nutritional Observatory* for 1953, an article by Dr. Rose (2) in which he outlined the progress in our knowledge of the amino acids during the first half of this century. It was a fascinating story he told, but a review of the early studies he cited (3, 4) makes it clear that, despite the classical contributions to our knowledge of amino acids and proteins by Kossel, Fischer, Abderhalden, Hopkins, Osborne, Mendel and Mueller and their colleagues there was, until after 1935, insufficient information even to demonstrate the intimate relationship between protein and amino acid requirements which we accept without question today.

After the discovery of threonine, it was possible to devise diets with amino acids substituted for protein which would support a reasonable rate of growth of laboratory animals and human infants and would maintain adult man in nitrogen equilibrium. This proved that protein nutrition was essentially amino acid nutrition and suggested that methodically performed growth and nitrogen balance studies could provide information from which a table of the amino acid requirements of different species of animals could be prepared.

Table 1, adapted from a recent paper by Block (5), is based on such studies. It lists the amino acid requirements for several species of animals as a percentage of the diet. We could add a column for various other species. Such tables are useful. They are prepared from the best estimates we have of amino acid requirements. They enable us to calculate, within reasonable limits, the nutritional adequacy of dietary proteins for which we have amino acid analyses. They enable us, again within reasonable limits, to prepare diets that will satisfy the amino acid requirements of various species of animals.

It is usually comforting to find such tables and, if we were naive, we might say, 'Here we have the amino acid requirements,' and overlook the limitations of the values given. Seldom, in such a table, is an estimate of the probable error of each requirement included and seldom is there adequate discussion of the factors that influence the requirements. Consideration of such factors makes it clear that amino acid and protein requirements and, even more so, ideal amino acid and protein intakes, can be defined only within rather narrow limits and it is this fact that I should like to discuss. I have selected four general topics as the basis for the discussion. These are: *1*) limitations of methods used for determining requirements; *2*) limitations of methods of reporting requirements; *3*) physiological factors that influence requirements; *4*) dietary factors that influence requirements.

The discussion cannot be detailed but I shall try to give an example or two under each heading.

LIMITATIONS OF METHODS USED FOR DETERMINING AMINO ACID AND PROTEIN REQUIREMENTS

a) *Growth.* The amino acid requirements of the growing animal are usually determined by measuring the minimum amount of an amino acid required, in an otherwise com-

TABLE 1. APPROXIMATE REQUIREMENTS OF VARIOUS SPECIES FOR INDISPENSABLE AMINO ACIDS (EXPRESSED AS PER CENT OF A DIET CONTAINING SUFFICIENT DISPENSABLE AMINO ACIDS)

	Rat		Young Pig	Adult Dog	Adult Human	Young Chicken
	Young	Adult				
Arginine	0.2	0	0.3	0.4	0.0	1.2
Histidine	0.4	0.1	0.4	0.1	0.0	0.3
Lysine	1.0	0.2	1.1	0.5	0.6	0.9
Tryptophan	0.2	0.1	0.2	0.1	0.2	0.2
Phenylalanine	0.9	0.2	0.7	0.6	0.9	0.9
Methionine + cystine	0.8	0.3	0.8	0.5	0.9	0.5
Threonine	0.5	0.3	0.6	0.5	0.4	0.6
Leucine	0.8	0.3	1.2	0.8	0.9	1.4
Isoleucine	0.5	0.5	0.6	0.5	0.6	0.6
Valine	0.7	0.4	0.6	0.7	0.6	0.8
Glycine	0	0			0	1.5

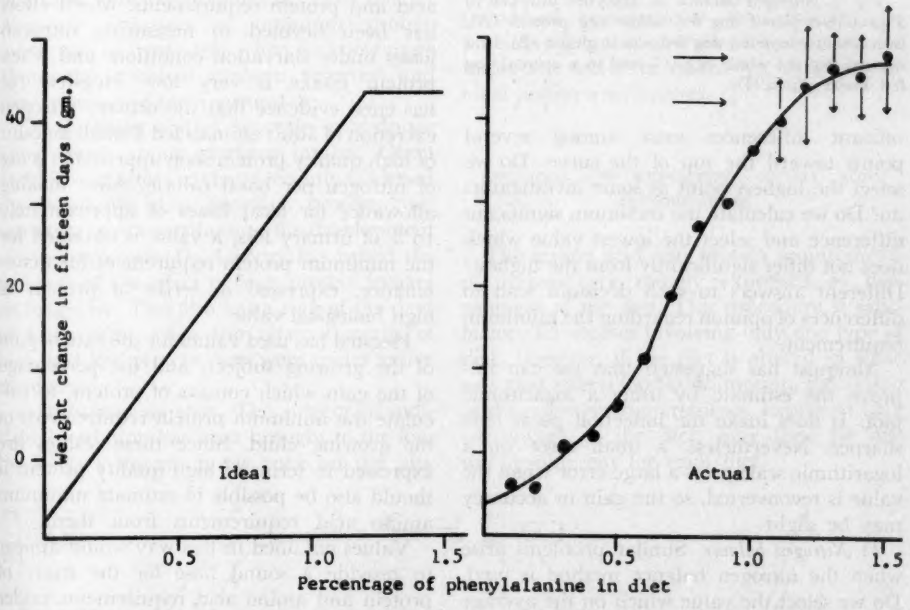


FIG. 1. Ideal and actual growth curves for phenylalanine requirement of the rat (after Armstrong, ref. 6).

plete diet, to support the maximum rate of growth—and I use the term 'maximum' with some reservation. For the adult animal it is taken as the minimum amount required to maintain nitrogen equilibrium. Such determinations provide us with a curve of the type shown in figure 1 (6). This is a plot of growth response against increments of the amino acid limiting for growth.

For a chemical or physical reaction we would expect a curve such as that shown on your left, with a sharp inflection point which can be measured accurately. For biological systems, however, the inflection point represents the summation of many reactions and is seldom if ever sharp, as can be seen from the curve shown on your right which was plotted from experimental results. The vertical arrows represent the standard errors of the points plotted.

It thus becomes a somewhat subjective decision as to which point on the curve should be selected as the requirement. Statistical analyses may indicate that no sig-

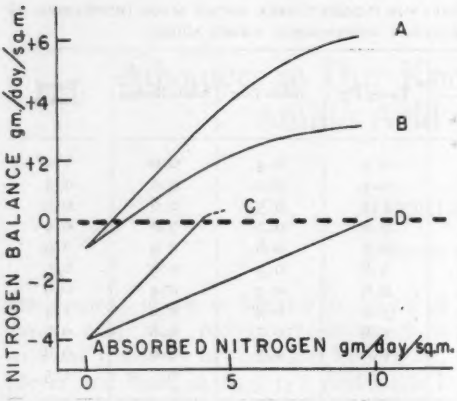


FIG. 2. Nitrogen balance vs. absorbed nitrogen in a protein-depleted dog fed whole egg protein (A), in a protein-depleted dog fed wheat gluten (B), in a normal dog fed whole egg (C) and in a normal dog fed wheat gluten (D).

nificant differences exist among several points toward the top of the curve. Do we select the highest point as some investigators do? Do we calculate the minimum significant difference and select the lowest value which does not differ significantly from the highest? Different answers to such decisions lead to differences of opinion regarding the minimum requirement.

Almquist has suggested that we can improve the estimate by using a logarithmic plot. It does make the inflection point look sharper. Nevertheless, a small error on a logarithmic scale gives a large error when the value is reconverted, so the gain in accuracy may be slight.

b) Nitrogen balance. Similar problems arise when the nitrogen balance method is used. Do we select the value which on the average will maintain equilibrium? Or do we select the lowest value which will give a slight positive balance? A difference of opinion on this point may be responsible for some of the differences in the estimates of the amino acid requirements of adult man (7).

The balance technique is also subject to other criticisms (8). It is influenced by the nutritional status of the individual. We know that given sufficient time a subject will eventually come into balance on a very low protein diet. This may require weeks if he has previously been consuming a large quantity of protein; it may be a few days if he has been eating little protein. Thus the duration of the experiment and the nutritional status of the subject can influence the results of nitrogen balance experiments and may lead to divergence of opinion regarding requirements.

Figure 2, taken from one of Dr. Allison's papers (8), illustrates this point. The distance between the points at which curve A and curve C cross the line representing nitrogen equilibrium gives a measure of the difference between the protein requirements of the depleted and the nondepleted dog as measured by the nitrogen balance technique.

c) Minimum requirements. This brings us logically to the question of minimum amino acid and protein requirements. Much effort has been devoted to measuring nitrogen losses under starvation conditions and when protein intake is very low. Hegsted (9) has cited evidence that the urinary nitrogen excretion of adult animals fed a small amount of high quality protein soon approaches 2 mg of nitrogen per basal calorie. After making allowance for fecal losses of approximately 10% of urinary loss, a value is obtained for the minimum protein requirement for maintenance, expressed in terms of protein of high biological value.

Hegsted has used values for the rate of gain of the growing subject, and the percentage of the gain which consists of protein, to calculate the minimum protein requirements of the growing child. Since these values are expressed in terms of high quality protein it should also be possible to estimate minimum amino acid requirements from them.

Values obtained in this way would appear to provide a sound base for the study of protein and amino acid requirements under various other conditions.

d) Minimum versus optimum. These are of course minimum values and how to determine the difference between the minimum and the optimum protein requirement is a problem which continues to plague nutritionists. It was discussed at length during the early part of this century particularly by Chittenden and has again begun to receive attention as indicated by yesterday's discussions by Dr. Wilson, Dr. Stevenson and Dr. György. We have become conscious of the fact that the body contains certain labile protein fractions which are lost during periods of low

TABLE 2. INDIVIDUAL VARIATION IN THE TRYPTOPHAN REQUIREMENT OF ADULT MEN (AFTER ROSE ET AL., REF. 11)

Subject	Tryptophan Requirement
	gm/day
R. J. D.	0.15
I. R. H.	0.15
15 young men	not over 0.20
R. E. F.	0.25

protein intake. Although we are aware of them, we know little of their significance. It is generally accepted that protein or amino acid intakes should be somewhat above the minimum, but the question is, 'How much?' Accurate estimates of optimum protein intake can be made only when we know more about the so-called 'protein reserves' and how to measure them accurately.

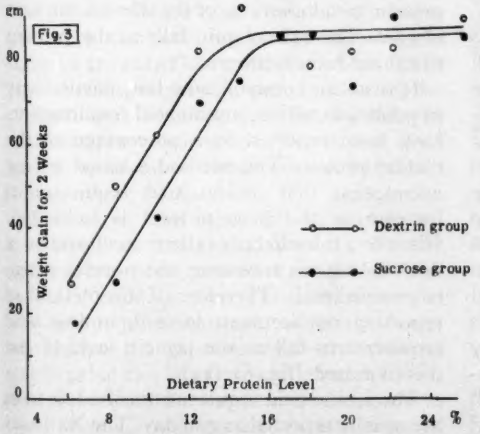
On the other end of the scale—nor do we know much about excessive intakes. Olson and his associates (10) have recently discussed the possibility that excessive protein consumption may contribute to the development of atherosclerosis. Dr. György has raised the question of the effect of high protein intakes on longevity. This also has a ring of the days of Chittenden when the relative merits of high and low protein diets were under active discussion.

e) Individual variation. The subject of individual variation has been brought to the fore by R. J. Williams in his book on the biochemistry of the individual. The results of animal experiments are usually presented as averages, and the individual variations, which are known to be wide, are usually masked. In experiments on man, costly experiments with relatively few subjects, individuals usually replace groups. The possible extent of individual variation is indicated in Rose's study on the tryptophan requirement of man (table 2) (11). In this case although more than 15 subjects had requirements of less than 0.2 gm/day, one was as high as 0.25 gm/day, and two were definitely as low as 0.15 gm/day.

If requirements vary to this extent one may ask, as Rose has, what percentage of the individual requirements may deviate appreciably from the average. This becomes an important factor in estimating optimum or ideal amino acid intakes.

METHODS OF REPORTING AMINO ACID REQUIREMENTS

The amino acid and protein requirements of animals are usually expressed as percentages of the diet. This procedure is satisfactory for studies involving only one type of diet; however, if the diet is altered in some way that affects food consumption, the amino acid or protein requirements, expressed as a percentage of the diet, may then be distinctly different for each diet.



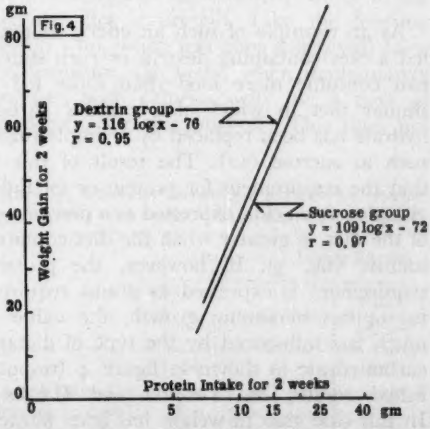


FIG. 3. Relation between weight gain and dietary protein level. Casein was supplemented with methionine.
FIG. 4. Relation between weight gain and protein intake. Supplemented casein was used as protein source.

FIG. 5

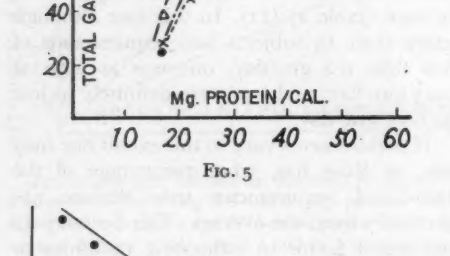


FIG. 6

As an example of such an effect, animals fed a diet containing dextrin or corn starch can consume more food than those fed a similar diet in which the complex carbohydrate has been replaced by a simple sugar such as sucrose (12). The result of this is that the requirement for protein or for individual amino acids, expressed as a percentage of the diet, is greater when the diet contains sucrose (fig. 3). If, however, the protein requirement is expressed as grams required to support maximum growth, the value is much less influenced by the type of dietary carbohydrate as shown in figure 4 (unpublished results, M. Yoshida and Harper). In this case gain in weight has been plotted against the logarithm of the protein intake

FIG. 7. Relation of dietary protein and dietary methionine + cystine requirements to age in days from birth of rats (*expt. 1.*) fed an adequate diet ad lib. (from Hartsook and Mitchell, ref. 16).

and the two curves shown are not statistically significantly different.

A similar effect is seen if the level of fat in the diet is altered. Animals eat primarily to satisfy their caloric needs. An increase in the fat content of the diet increases the caloric density of the diet and causes a drop in food intake. The amount of protein per calorie is also decreased when the fat level of the diet is raised and, therefore, the protein intake falls, even though the caloric intake may be unchanged. In order to maintain the protein to calorie ratio of a high fat diet at that required for maximum growth, the percentage of protein must be greater than that in a low fat diet.

Figure 5 shows the effect of varying the protein to calorie ratio of the diet on the rate of gain. The rate of gain falls as the protein to calorie ratio is lowered (13).

It is not so common now but, particularly in poultry nutrition, amino acid requirements have been reported as a percentage of the dietary protein. This method is based on the assumption that amino acid requirements increase as the protein level is increased. However, this effect is rather small and is of doubtful significance over the normal range of protein levels. Therefore, if this method of reporting requirements is used, amino acid requirements fall as the protein level of the diet is raised (fig. 6) (14).

The amino acid requirements of adult man are usually reported as gm/day. The National Research Council recommended allowances,

however, are expressed as gm/kg of body weight. Rose has reported that no relationship could be demonstrated, in experiments on adult man, between body weight and amino acid requirement. It is possible that variations in body composition might mask any relationship between protein intake and body weight. The relative proportion of fat to muscle would appear to be an important factor.

Stearns and her associates (15) in their studies on children have attempted to take this into account by relating requirement to active muscle mass as determined by creatinine excretion. However, this too offered no advantage in Rose's studies with adults.

Perhaps, if the minimum protein and amino acid requirement for maintenance can be related to the basal calorie requirement, it may be possible to devise some other base to which the increments needed for growth, protein repletion and other stresses can be related, so that we can develop a method of reporting amino acid and protein requirements which will be more generally applicable. This may be quite difficult for amino acids because some are used only for protein synthesis whereas others, such as methionine and tryptophan, enter into a variety of reactions in the body.

INFLUENCE OF PHYSIOLOGICAL STATE

a) Growth. Protein and amino acid requirements, as currently reported, vary with the stage of growth of the individual. During the period of rapid growth, protein is being deposited and requirements far exceed the maintenance requirement. This is well illustrated by a figure from one of Mitchell's studies (fig. 7) (16).

This shows the rapid fall in protein requirement as the animal matures. Similar figures have been presented for the requirements of children (17). This emphasizes the fact that requirements are constantly changing during the growing stage and that no single value can be given as the requirement, unless it is based on some criterion, such as body weight, muscle mass, surface area, or calorie requirement, which takes into account the factors responsible for the changes in the protein or amino acid requirements of the subject.

b) Lactation and reproduction. Our knowledge of the changes in protein and amino acid requirements during reproduction and lactation is scanty. Again, however, since protein is accumulating in the fetus or is being secreted in the milk, the requirements must increase. Again some increment above the basal requirements must be added to cover these needs as Dr. Wilson reported earlier.

c) Repletion. The adult who has suffered protein depletion as a result of starvation or some pathological condition requires an allowance for the repletion of wasted tissues. Again an increment above the maintenance requirement is necessary.

d) Work. There is little evidence, however, that work increases protein need, provided the supply of calories is adequate. This was demonstrated many years ago and is illustrated by some observations of Shaffer (table 3) (18). These subjects were consuming only between 35 and 40 grams of protein per day. They showed no evidence of increased protein catabolism during a period of work.

e) Calorie intake. The relationship between caloric intake and protein need has been extensively studied (19, 20). It is well known that the demand for calories is a primary demand and that if insufficient calories, as carbohydrate or fat, are provided, other materials will be used instead. The only other material in significant quantity in the average diet is protein. Like the freezing person who, when fuel runs short, will burn the furniture, the body, when inadequately supplied with calories, will use a part of its protein for this purpose. This does not

TABLE 3. URINARY NITROGEN EXCRETION DURING REST AND AFTER WORK (FROM SHAFFER, REF. 18)

	Intake		Urinary Nitrogen	
	N	Calories	Total	NH_3 + creat. + uric acid
	gm		*gm*	*gm*
Rest (6 days)	5·9	2300	4·77	1.06
Normal (5 days)	6.0	3000	4.40	1.08
Work (4 days)	5·9	3200	3·94	1.10

mean that the protein requirement is increased during periods of caloric restriction but that some of the protein is diverted from its normal use in protein synthesis to serve as a source of calories.

INFLUENCE OF TYPE OF DIET ON PROTEIN REQUIREMENT

a) Effect of type of carbohydrate, level of fat and protein-calorie ratio. The effect of the type of carbohydrate, the level of fat and the protein to calorie ratio have already been mentioned. Although the type of dietary carbohydrate and the dietary level of fat may affect food consumption and, thereby, protein intake, they appear to affect the requirement substantially only when it is expressed as a percentage of the diet or in some similar way. They do not, for example, appear to alter the protein requirement expressed in absolute terms such as gm required to support maximum rate of gain.

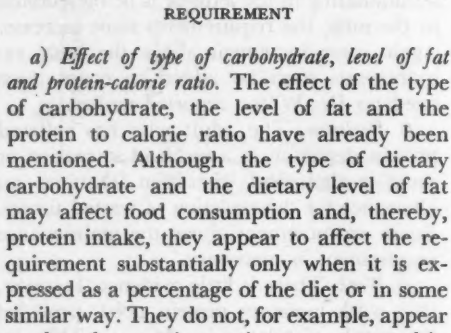


FIG. 8. Effect of protein level on lysine requirement of chicks (after Grau, ref. 21).

b) Protein level. There is some evidence that amino acid requirements increase as the level of dietary protein is increased. A figure taken from a paper by Grau illustrates this (fig. 8) (21).

One must be careful in appraising these observations, however. Although the requirement for lysine, expressed as a percentage of the diet, increases as the protein level is increased, most of the curves shown are for animals consuming diets that are inadequate in protein. It is therefore only logical that if we have two limiting factors such as protein and lysine the need for lysine will increase until protein, as such, becomes limiting. Then, if the protein level is further increased, more lysine can be utilized until protein again becomes limiting. This is not actually an increase in the requirement. Nevertheless, there does come a point at which it is possible to demonstrate that an adequate diet is made less adequate if the over-all protein level is increased while the level of one amino acid is held constant.

It should be noted that the method of studying the effect of protein level on amino acid requirements is almost the same as that used for studying amino acid imbalances and is subject to the same interpretations.

c) Amino acid imbalance and antagonism. This leads us to the subject of amino acid balance and imbalance, another dietary factor that may influence amino acid requirements. But first we should clarify our usage of these terms.

The idea of amino acid balance arose from the fact that the indispensable amino acids are needed in different amounts in the diet. Proteins that provide the indispensable amino acids in the proportions in which they

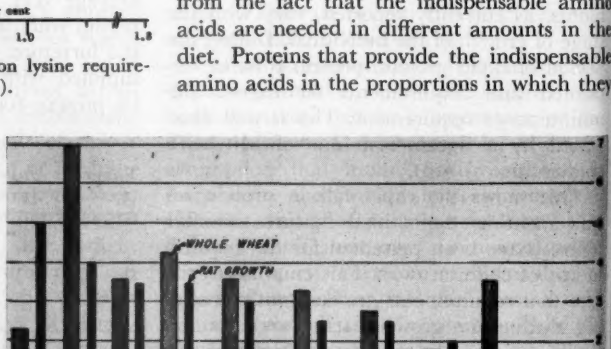


FIG. 9. Amino acid proportions in whole wheat protein (calculated on basis that tryptophan = 1.0) compared with proportions utilized in rat growth (from Flodin, ref. 22).

are required are said to be well-balanced. Well-balanced proteins, proteins in which the indispensable amino acids occur in the ideal proportions, are required in minimal quantity to satisfy the amino acid requirements of the animal. The further the proportions of the amino acids in a protein deviate from the ideal, the more of that protein is required to satisfy the amino acid requirements.

In figure 9 (22), the proportional amino acid requirements of the rat are shown as black bars. Proteins in which the amino acid proportions resemble this pattern are well balanced. The other bars represent the amino acid proportions in wheat proteins. Here the relative amount of lysine is low; therefore, this is an unbalanced protein and must be consumed in much larger amounts than is the case for well-balanced proteins, if the lysine requirement is to be satisfied.

A situation may arise, if a protein or a diet is sufficiently out of balance, so that the animal is unable to eat enough of the protein to satisfy its amino acid requirements. Also a stage may be reached if the balance is sufficiently poor so that there is a fall, beyond what is expected, in the efficiency with which the protein is used.

This leads us to the concept of amino acid imbalance which may be defined roughly as an adverse effect, usually seen as a depression in growth, which results from an alteration in the amino acid balance of the diet. Such effects can readily be produced by adding to a diet an amino acid mixture or a protein that lacks one of the essential amino acids. For example (table 4) (unpublished results, A. E. Harper), when a tryptophan-deficient protein such as gelatin is added to a diet containing casein, unless tryptophan is also added, growth may fall below that obtained with the unsupplemented diet. Such imbalances, as we call them, have the effect of increasing the requirement for the most limiting amino acid.

Table 5 shows the effect on the need for threonine of supplementing a diet containing casein with 4% of an amino acid mixture lacking threonine (unpublished results, A. E. Harper). The amino acid mixture causes an imbalance which results in a growth depression. An additional 0.05% of L-threonine is required to improve the balance and restore the growth rate to the original value. In this case the total intake of threonine has to be increased to restore growth.

TABLE 4. EFFECT OF ADDITIONAL GELATIN ON GROWTH OF RATS FED ON DIETS CONTAINING 6% OF CASEIN, METHIONINE (0.2), DEXTRIN AND ADEQUATE NIACIN

Dietary Additions	Average Gain
	gm/2 wk
1. None	27
2. DL-threonine, 0.2%	43
3. 3% gelatin	36
4. 6% gelatin	27
5. 12% gelatin	13
6. 12% gelatin + 0.2% DL-tryptophan	47

TABLE 5. EFFECT OF AMINO ACID IMBALANCE ON UTILIZATION OF THREONINE BY RATS FED A DIET CONTAINING 6% OF CASEIN AND 0.3% OF DL-METHIONINE

Diet			Av. Gain in 2 Weeks
Casein	A.A. mix minus threonine	L-threonine	
%	%	%	*gm*
6			19±3
6	4		11±1
6	4	0.025	11±2
6	4	0.05	21±3
6	4	0.10	42±3

An excess of a single amino acid may also cause a growth depression and result in an increased need for one or more other amino acids. We (23) have observed one case in which an excess of leucine causes an increase in the requirement for isoleucine. This can be demonstrated when isoleucine is not the most limiting amino acid in the diet and appears to be a specific antagonism of the utilization of isoleucine by an excess of leucine. This is illustrated in figure 10 in which the open circles represent the growth increments observed when rats are fed an isoleucine-deficient diet supplemented with graded levels of isoleucine. The solid circles represent the growth increments when in addition to the increments of isoleucine, 2% of L-leucine is added as well. At each level of isoleucine except the highest, the addition of 2% of L-leucine causes a growth depression.

d) Dispensable amino acids. Finally we should say a word about the relationship between dispensable and indispensable amino acids. At

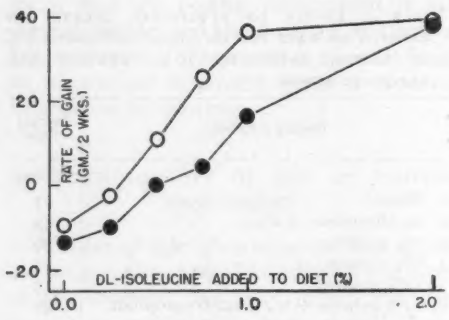


FIG. 10

TABLE 6. GROWTH OF RATS FED ON DIETS CONTAINING DEXTRIN AND 6% OF CASEIN SUPPLEMENTED WITH AMINO ACIDS

Diet		Rate of Gain
Casein	Amino acid mixture	
%		*gm/2 wks*
12	0.2% L-cystine	40±1
6	Complete amino acid mixture	39±2
6	Amino acid mixture—arginine	31±2
6	Amino acid mixture—glutamic	29±1
6	Amino acid mixture—lysine	21±1

the beginning I stated that the early work with diets in which crystalline amino acids were substituted for protein indicated that protein nutrition was essentially amino acid nutrition. It soon became apparent, however, that protein nutrition involved more than merely satisfying the requirements of the animal or the subject for indispensable amino acids. Some other source of nitrogen was also required. A quantity of the dispensable amino acids or even ammonium salts could serve this purpose, however, the amino acids appear preferable (24). Recently we have found that even with a low level of protein in the diet some additional dispensable amino acids may be required (unpublished data, A. E. Harper). Similar observations have been made by Dr. Holt in his studies on the amino acid requirements of children.

From the results in table 6 it can be seen that the omission of glutamic acid from the diet containing casein and an amino acid mixture caused a growth depression.

This and the other work on the subject makes it clear that more than just the indispensable amino acids must be considered, and that amino acid requirements must be measured using diets that contain an adequate supply of nitrogen from the dispensable amino acids.

e) Protein requirements. However, when we talk of protein requirements this factor is of little importance because dispensable amino acids make up at least 40% of the amino acids in proteins. Nevertheless, other factors besides those previously discussed must be kept in mind in studying protein requirements. The amino acids of some proteins are not readily released in the gastrointestinal tract so allowance must be made for differences in protein digestibility. Also proteins are not all of equal biological value—that is, they are not all equally well balanced—so allowance must also be made for differences in biological value. Usually protein requirements are expressed in terms of a highly digestible protein of high biological value. For less digestible proteins of lower biological value the requirement, of course, is higher.

In conclusion, amino acid and protein requirements as they are currently reported are relative rather than absolute. They may be influenced by such factors as: the accuracy of the method used in determining the requirements, the method of reporting the requirements, the physiological state of the experimental subjects, and the nature of the diet. The effects of some of these factors are only apparent and may be considered as artifacts of the methods used, others are real and represent true changes in protein or amino acid requirements. What we need, perhaps more than anything else, in this field of study, is some basis for reporting requirements so the values presented are relatively little influenced by the various factors that have been mentioned.

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PANEL DISCUSSION ON NUTRITION EDUCATION

Introduction

E. NEIGE TODHUNTER

University of Alabama

YESTERDAY we had a very stimulating day hearing the findings on research about nutritional needs of people. This morning we learned of the problems in the underdeveloped areas of the world, and it was stressed to us that there was no need for nutrition education. This afternoon's program is a logical climax to the discussions that we have been having. We are not an underdeveloped country from any point of view but we do have, I think you will agree, a need for nutrition education here in this wonderful country of ours. Therefore our discussions this afternoon are concerned with this problem of how to get nutrition information to people, how to make available the knowledge we have about nutrition, and how to make it function in the lives of people.

It is exciting and it is a most satisfying experience to work in the laboratory, to be one of that group doing research and making the discoveries, and particularly is that true of basic research such as we had the latter part of this morning. But I would go so far as to say that research has its real value only when the findings are applied to the benefit of individuals and families; that is, when we put nutrition information to use. We need to put it to use in this country for the public, for the young homemaker starting out to take care first of a newly acquired husband and then thinking in terms of a future family; for the mother of a family; for the older age group; and for all the individuals who make up our public.

From what you and I see and know, we can tell there is still much need of nutrition education. In the schools the young child, and perhaps even more so the teenager needs our help. The professional educator, the home economist, the dietitian, the public health worker, the teacher—all of these have a tremendous job to do in educating others in the areas of nutrition and they need to have a reliable background of training as well as skill and ability in interpreting the information that they have.

Another group that we look to, the medical profession, has a remarkable opportunity which is not yet being met to nearly the extent it should be—a great opportunity to reach the public with valuable and helpful guides regarding nutrition. These are the groups that we are going to hear some suggestions for this afternoon from our speakers, as to how we may deal with these problems.

We are, of course, dealing with food for people, and that is the one commodity that everyone must have. It is big business for agriculture, for industry, for the food processors and the manufacturers. And it also, unfortunately, is a very profitable business for the quacks and the faddists who enrich themselves through misleading the public, selling products that are wasteful of the consumer's money and at times even harmful to the consumer.

So, you might sum it up that our present responsibility is combating misinformation and, secondly, presenting sound nutrition information for people of all ages, everywhere in our population.

This is not an easy problem. A generation or two ago, if you heard voices you were considered queer and possibly were 'taken care of.' Now you cannot escape voices; they come at you from every side. From radio and TV, come contradictory and confusing voices, and from the printed word come seductive, glamorous stories that promise you all if you will just 'use our pill, our product, our whatever it is' that is being sold. And then there are

those beautiful colored pictures that you see of foods of every kind and especially of the pies and the cakes—those foods that seem to do something to the figure if they don't do much else for you. These are the distractions; these are some of the forces that are operating in our nutrition world today; and we need to find some way of combating, or at least offsetting their influence.

You know, the early mariners thought they had the greatest trouble that any group could have in passing through the Strait of Messina. You remember on one side was the rock Scylla and on the other side the whirlpool Charybdis. The homemaker today has a worse problem. She not only has to avoid the rock of ignorance and the whirlpool of misinformation, but she has to steer her way through the carefully planned temptations of the supermarket or down the cafeteria counter. How to steer this course, how to shut out the voices, how to select wisely from the information that comes in on all sides—these are some of the problems that face us and these are some of the problems that our panel is going to help us with this afternoon. They are experienced workers in this difficult field of nutrition education.

Nutrition Education—Progress and Problems

A. M. BEEUWKES

University of Michigan

WE HAVE SO FEW traditions to guide us in nutrition education for we are living in a society attempting to adapt to an ever-changing food environment. "The history of our civilization does not record a time when change was so rapid, or so enmeshed in a growing complexity of scientific, physical, social, psychological and cultural influence" (1).

From the beginning of time, man's struggle to obtain food and his pleasure in eating it have provided a purpose in life. Our attempt to understand food as a science, however, is a venture of this age. The science of nutrition has unravelled a part of the immense fabric which nature holds in a tantalizing manner before the creative minds of our research workers. What we have learned represents progress. The vast areas of the unknown in the science of nutrition, however, excite the imagination for if the next half century is as productive research-wise surely we need beg for tolerance on the part of the workers who in the year 2000 wonder why we did not better comprehend what to them had become so obvious.

But progress in the science of nutrition has created problems in nutrition education. People treasure their independence in making food selections and all persons feel some degree of security in their own food practices for eating is such a commonplace experience. And through the centuries, man has hoped that health, long life, freedom from disease and suffering might someday be assured him through the ingestion of particular foods. Consequently, as the science of nutrition has enlarged our understanding of the relation of food to health, many people have clutched at each straw in the wind as if it were the whole answer to all of their hopes. Scientists have not promised nor even suggested outcomes which research has not proved reasonable in the field of human nutrition. But the American public evidences a willingness, even an eagerness, to be exposed to and to share in the newer knowledge of nutrition. This attitude creates a favorable climate for a positive program of nutrition education; it also provides the faddists with an eager and gullible audience.

Progress in the science of nutrition has created the problem of learning how to provide truly effective programs in nutrition education. To this date, our programs have not adequately bridged the gap between scientific advances and the food practices of our people. This is not to imply that there has been a lack of sincerity or effort on the part of professional and industrial leaders. In fact, nutrition education has made great strides within the past quarter of a century. But our accomplishments as measured in changing food consumption patterns have provided us with evidence that our programs are not fulfilling the objectives we have set.

MORE EFFECTIVE PROGRAM IN NUTRITION EDUCATION NEEDED

With no thought of completeness, I will mention a few of the many reasons why a more effective program in nutrition education is needed and point out some problems that have resulted from progress in nutrition research.

1) Industry continually provides us with a greater variety of foods and combinations of foods, processed and packaged in new and novel ways. Product development, however, proceeds much more rapidly than consumer understanding of the role each of the foods can play in a well-planned diet. This presents an educational problem.

2) "It is no longer realistic to inquire whether mothers of young children should work. Many of them are working—in fact,

some seven million with children under 18. Of every four women in the labor force, one is a mother with one or more minor children. Moreover, 2.5 million of these mothers have children under 6" (1). Traditionally, we have looked to mothers to guide their children in the acquaintance with and acceptance of a variety of foods. With women assuming the dual role of homemaker and wage earner, mothers are assigning the responsibility of guidance in the development of their children's food habits to others.

3) Although we suggest that schools increase their role in nutrition education, we need to remind ourselves that the drop-out rate for the United States is approximately 50%. In Michigan, for example, for every 100 children who begin the first grade, only 60–65 complete the twelfth grade. Consequently, all children are not available for nutrition education throughout all of the 12 years. Furthermore, nutrition education is not an accepted part of the curriculum in many of the teacher education colleges. Although public health nutritionists, colleges and universities have made valiant efforts to provide in-service nutrition education for teachers the need is so great that our efforts need support and expansion.

4) Dietary surveys and nutritional status studies leave little doubt that improvement of the dietary habits of our teen-age girls represents an immediate and serious challenge. To meet the nutritional needs of normal growth and development is problem enough. But, during the years 1950-55, 12% of the live births were to women under the age of 20. And what is even more significant is that more than one third of all first births were to women under 20 years of age. It is in preparation for the first pregnancy when education may accomplish the most. To superimpose the additional requirements of pregnancy and lactation on the increased needs during adolescence requires nutrition education par excellence.

5) Educational material prepared and distributed by industry has a tremendous potential contribution because of its excellent format and reliable information (if from reliable sources) and its availability. But, it frequently cannot be used effectively because of its fragmentary nature. Some of the educational material places particular emphasis on a single food and many teachers do not have the knowledge necessary to be selective so that children will learn how foods complement each other. Also, there is an abundance of teaching material about some foods—oranges and milk, for example. But there is little or nothing available about other foods which also deserve some consideration. Potatoes are an example of a food rarely advertised, and never glamorized.

6) The Food and Drug Administration estimates that our people are spending about one-half billion dollars a year for pills, panaceas and so-called food supplements. Obviously, the public is placing increasing reliance on pills and promises and simultaneously losing respect for food as a source of necessary nutrients. The role which food plays in the attainment and maintenance of good nutrition has been misinterpreted by those who seek to replace food with a pill and a pamphlet.

Vitamin concentrates, mineral supplements, etc. are medications which, valuable as they are in the field of medicine, cannot replace food. Consequently, too many of our people deny themselves the privilege and the pleasure of an adequate diet because in their ignorance they have been influenced by a fast-talking salesman who scorns the nutritive value of our food supply. On the other hand, some mothers have denied their infants a source of a needed vitamin because they gave little credence to vitamins under any circumstances. At the same time, reports of over-use of some vitamins concern us.

Obviously, this state of confusion permits neither food nor therapeutic supplements to be used to their best advantage. The confusion has arisen because the public has not received adequate assistance in understanding how their nutritional needs can be met within their economic and time limitations from our bountiful food supply nor have we successfully influenced our people to recognize an adequate diet as an important aspect of both preventive and therapeutic medicine.

7) The widespread dissemination of facts does not guarantee a change in practice. Dr. Jennie Rowntree has clearly stated this aspect of the problem. "A mass of facts about nutritive values and recommended allowances is no more nutrition than a pile of lumber is a house. The value of knowledge lies in its

possibilities. What can be done with it is all important."

These represent but a few of the reasons why a more effective program in nutrition education is needed today. Universities, professional organizations, government agencies and industry have each in their own way provided those of us in the field of nutrition education with information, encouragement and moral support. Publications of the Food and Nutrition Board of the National Research Council, the Council on Foods and Nutrition of the American Medical Association, the member groups of the Interagency Committee on Nutrition and the World Health Organization have served us well. *Nutritional Data*, supplied to us by the Heinz Company, is used so widely that it is difficult to imagine its absence from our ready reference shelf. Indeed, nutritionists do not want for a steady flow of information; we look for time enough to give a representative share of it our full attention. But—what we can do with this knowledge is all important. How can we more effectively motivate our people to apply knowledge which we are attempting to interpret?

WE NEED A NUTRITION EDUCATION FOUNDATION

I believe that the answer lies in the establishment of a Nutrition Education Foundation. I share this conviction with leaders in nutrition and in industry who have suggested that such a foundation could serve to guide and correlate our several independent efforts. Needs for nutrition education are so great and personnel prepared to provide it are so few that we can ill afford to duplicate our efforts or appear to compete for the public's interest and attention.

It is reassuring to note that representatives of both industry and education have stated their recognition of the need for a Nutrition Education Foundation. Dr. H. E. Robinson, Food Chemist with Swift and Company, in October 14, 1953 issue of *Agriculture and Food Chemistry* wrote: "Since the right kind of nutrition education is so badly needed in this country, it might be a sound endeavor for the food industry to form a Nutrition Education Foundation, conducted along the same lines of the high policy standards set by the Nutrition Foundation. In any event more must be done in furthering the interpretation to the consumer of the outstanding research findings in nutrition both theoretical and clinical, that have come forth in the last decade alone" (2).

Dr. G. Cullen Thomas, Vice President of General Mills, Inc., in May 1954, spoke at the Food Industries Committee of the Nutrition Foundation on the subject "Nutrition Education and Challenge." Dr. Thomas said: "Deepening and broadening our nutrition education efforts to give them greater stature and make them more effective calls for more intensive and aggressive action—and better coordination and guidance of these many efforts. The one vital factor we do not have and badly need is an authoritative agency to clear, coordinate and advise all who are striving to do a good nutrition education job. Nutrition education today needs the same sort of guidance and coordination that nutrition research has in the Nutrition Foundation. Nutrition education needs an authoritative clearing house. This clearing house must have both public respect and professional acceptance—scientific integrity and objectivity and educational stature" (3).

While Dr. William H. Sebrell was Director of the National Institutes of Health, United States Public Health Service, he spoke on the subject "Nutrition at the Shopping Center" at the National Food Conference in March 1955. Dr. Sebrell's summary statements were: "We will never have a really successful program until the food sellers and the food industries cooperate with the scientists, nutritionists and teachers in developing a positive, aggressive, coordinated program to present basic nutrition facts clearly and simply to the American housewife, so that she can use those facts at the point of sale for the best nutrition of her family. I am sure that if some such plan could be evolved it would prove to be good business practice and at the same time, make a significant contribution to public health" (4).

Miss Marjorie M. Heseltine, Chief, Nutrition Section of the U. S. Children's Bureau, spoke before the Association of State and Territorial Nutrition Directors at the annual meeting of the American Public Health Association in 1955, and said: "I am still enough of an optimist to look forward to the time

when a foundation supported by enlightened producers and processors of basic foods will support a unified program of nutrition education on the same high plane on which food and nutrition research is being financed at the present time."

The most recent appeal for coordinated efforts was made by the two hundred professional workers who attended the Nutrition Education Conference held in Washington, April 1–3, 1957. The purpose of the Conference was to focus attention on nutrition education and to consider ways to make it more effective. The Conference urged cooperation and coordination of efforts by all involved in nutrition education and stated that one of the unsolved problems was "provision of a clearing house to help the public get more accurate nutrition information" (5).

The organization of a Nutrition Education Foundation will require vision, courage and the conviction that our coordinated efforts could make a greater contribution than the sum total of our individual endeavors. No single food can provide all of the nutrients necessary for good nutrition. No single agency, professional group or food industry working alone can effectively motivate the public to share our dedication to the belief that good nutrition is basic to health and that without health, security and happiness are beyond reach.

The ways in which a Nutrition Education Foundation could serve our needs are so many that it will be difficult to determine just where and how to begin. The complexity of the problem will require the skill and knowledge of all the professions that can contribute to an interdisciplinary approach in nutrition education. Our present programs might be likened to the solo instruments in a symphony orchestra and we are in need of a director who will bring together in harmony the contribution of all groups who have found themselves playing a solo part when the score called for a full orchestra.

SUMMARY

In summary, as the science of nutrition continually expands, we find ourselves more and more concerned with our inability to fill an ever-widening gap between what is known and what is practiced. We need a coordinated, interdisciplinary approach so that the biological and social sciences together can assist us to better understand not only what to teach but how and when to accomplish it.

A Nutrition Education Foundation could provide the same sort of guidance and coordination in education that nutrition research has in the Nutrition Foundation under the brilliant leadership of Dr. Charles Glen King. Our host, Henry J. Heinz II, is currently serving as President of the Nutrition Foundation.

Progress will always create problems. Working together, however, our program in nutrition education should help the public benefit from the progress in the science of nutrition without needing to suffer through the problems which lack of understanding has brought in its wake.

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Successful Nutrition Education in Elementary Schools

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COMPARED to some other sciences, nutrition is a relatively young science. However, important generalizations have been developed with regard to the way that the body utilizes food and the needs of the body for various kinds of food if good health is to be achieved. Reliable information concerning the nutritional value of specific foods has been made available. These broad generalizations and the tested information provide the foundation on which programs of nutrition education can be built.

Nutrition is a science with great potential for human good. If the broad generalizations and tested information are utilized, it can help people to lead healthier, happier lives. In some cases, the results of nutrition research can be utilized by community agencies and institutions in planning their feeding programs. Food manufacturers can and have improved their products to make certain nutrients available to the public at large. But, the major task is for people in general to weave what we know about nutrition into their patterns of living. This is the goal of those concerned with nutrition education. Certainly, to develop effective nutrition education programs in elementary schools will be an important part of this task.

Many children and adults are not eating the foods that are needed for healthy, happy living. In many parts of the world, there are large numbers of children suffering from severe malnutrition. These children have little resistance to disease and often are doomed to die at an early age. In the United States the number of children suffering from severe malnutrition has declined. In 1936 a third of the diets studied by the United States Agricultural Marketing Service and the United States Agricultural Research Service were classed as 'poor.' In their 1955 survey as few as 10% of the diets could be classed as poor (1). However, in a study of the breakfast habits of children in two elementary schools in New Jersey in 1958 (2), only 20% of the children reported eating a breakfast that could be rated adequate as recommended by the National Research Council. Thirty per cent of the reports had to be classified as poor and 45–50% of the reports were classified as inadequate. Of special interest to nutrition educators is the report that "Relatively little improvement in urban dietary levels has taken place since 1948" (1). Most of the road is ahead for the nutrition educator.

For effective nutrition education, patterns of behavior must be changed. Usually, our patterns of eating are deep-set, i.e. they are habits. Often the individual's ways of eating are almost automatic, and very little deliberation is devoted to what and how we should eat. Habits can be changed, but it is difficult and usually requires conscious personal involvement over a period of time.

Most of our habits are formed when we are young, and children's habits are more easily changed than the habits of older people. A number of careful studies support our common sense observations that it is easiest to develop new and better habits when a child is young. This is one of the important arguments for increasing our efforts in nutrition education in the elementary schools (3, 4).

Good nutrition early in life is essential for the proper growth and development of the human body. During the elementary school years, children are going through a period of steady growth. They are building muscles, developing coordination and using a great deal of energy. The teeth and bone structure are in a vital stage of development. Good nutrition in childhood lays the foundation for good health in later years.

RESOURCES FOR NUTRITION EDUCATION

The family, various community agencies and the schools are institutions in the community that contribute to nutrition education. To help everyone achieve adequate nutrition, the efforts of all of these institutions are needed.

The family. The family is the most basic educational institution. In the family the young child is guarded and nurtured during the critical early years of life. From parents and other members of the family, children learn the basic habits that are needed to survive. Some of these habits may be contrary to reliable research findings, but, in environments where survival calls for continual struggle, these habits are a part of the child's cultural heritage and extremely difficult to change.

As an educational institution the family serves primarily to transmit culture, not to change it. The nutrition of infants and young children can be changed through work with parents. The cooperation of parents is needed by other institutions that try to change patterns of eating. After all, children cannot eat foods that are not made available to them. Although the family is primarily an institution for cultural transmission rather than change, other institutions that try to change habits must have the cooperation of parents.

Community agencies. A number of community agencies such as departments of health, maternal child care centers and agricultural extension services are concerned with nutrition education. Such agencies often have direct contact with individuals, and many of them have developed and produced very fine teaching materials. Usually, these agencies work with adults. Through their work with adults they can indirectly influence the patterns of eating of children. Sometimes they can provide resource materials and consultation services for teachers and school administrators who work with children.

Elementary schools. Elementary schools are community institutions which are designed to help each individual child to achieve optimum intellectual, physical and social growth and development. As children are encouraged and helped to grow and develop they become better citizens of the communities that support the schools.

Nutrition education is an important part of education for growth and development. Its contribution to physical development seems obvious. In addition, adequate nutrition appears to be important for optimum intellectual development. The child who is frequently absent because of colds and minor illnesses, works under a handicap in the elementary school. The children who begin to fidget and squirm around at eleven in the morning may have had no breakfast that morning. In some elementary schools work on the skill subjects has had to be restricted to fairly short periods of time when the children are able to concentrate upon their work. The experience of many teachers indicates that children with poor or inadequate nutrition are at a disadvantage on the playground, in the gymnasium and in the classroom.

Some kinds of learning can take place better in the elementary schools than anywhere else. Often, children teach each other. An elementary school administrator's child steadfastly refused to eat certain kinds of foods. The administrator was keenly aware of the importance of good nutrition and tried in a number of ways to induce his children to eat the foods he knew they needed but with little success. However, this child had a teacher who ate with her children in the school lunchroom. She encouraged the children to try different kinds of foods. Of perhaps greater importance, to eat these foods became 'the thing to do' among those children. The administrator was pleasantly surprised to see that his child learned in school patterns of eating that he and his wife had been unable to develop with their children at home.

Two major problems face us in the development of nutrition education in elementary schools. One is to call to the attention of teachers and administrators the importance of nutrition education for children. Teachers and administrators are professionally concerned with the growth and development of children. But, elementary school classrooms are often filled to overflowing, the curriculum is crowded, and great demands are made upon the time

and energies of teachers and administrators. Most teachers and administrators have had little or no contact with nutrition as a science and are not aware of the contributions that can be made through nutrition education. The second problem is the never-ending problem of improving our methods and materials for effective nutrition education. In this paper an approach to nutrition education in the elementary school is suggested that may have some promise.

EDUCATION TO MEET THE NUTRITIONAL NEEDS OF CHILDREN

One of the most promising approaches to nutrition education in the elementary school is to plan experiences to meet specific nutritional needs of children. Many youngsters eat insufficient amounts of green and yellow vegetables. Others may not drink enough milk. In too many cases we find that children do not have enough nourishment before coming to school in the morning. There are a variety of experiences that can be planned by teachers to help children overcome some of these deficiencies (5).

The process of making a study of nutritional needs can contribute to the nutrition education of children. Children become aware that someone is concerned about the kinds of foods they eat; for the first time, perhaps, they may realize that this is of some importance. They will become conscious of what they actually are eating; they may be led to ask, "What kinds of food should I eat?"

Study of the Nutritional Needs of Children

Several procedures are available to teachers and administrators to help them make a qualitative appraisal of the nutritional needs of children. These procedures can be used by classroom teachers. The cooperation of parents and the help and advice of school nurses, doctors, special teachers and consultants can make these procedures more effective.

1) *Daily observation of children.* The sensitive teacher can gain considerable information concerning the nutritional needs of children by observing the children eating in the lunchroom, working in the classroom and at play on the playground. Sometimes, they will see children that have firm, well-developed muscles, well-formed teeth, erect posture, bright, clear eyes and the other physical characteristics of the well-nourished child. Too often, they will see children that have a poor appetite, are chronically fatigued, have poor posture and flabby muscles and other physical characteristics that may be due to inadequate nutrition. Children's contributions to discussion, their drawings and paintings and their general behavior may give indications of nutritional needs. The teacher may find out the kinds of foods the child does or does not eat, what meals are frequently skipped and whether a child has marked likes or dislikes for foods. The teacher will make special note of questions that children raise concerning foods.

2) *Study of school health records.* From the school health records, the teacher can obtain information concerning the child's rate of growth over a period of time. A record of minor illnesses, sporadic school attendance and high incidence of dental caries may have implications for nutrition education.

3) *Diet surveys.* Simple diet surveys interpreted qualitatively can give the teacher information about the kinds of foods the children do or do not eat, the regularity of meals and the children's ability to identify and report the food that they eat. The eating patterns revealed by the diet surveys indicate directions for the teacher in planning nutrition education experiences.

Children in the upper grades who have learned to read and write can report on paper what they have eaten for breakfast. This information has to be obtained from younger children through interviews. To make it a task of manageable proportions for the classroom teacher, we have suggested that every third child in the class be interviewed. The information from reports and interviews is augmented by careful observation of patterns of eating in the school lunchroom.

Activities to Help Meet Nutritional Needs

A wide range of activities is available for teachers to develop with children to help

meet the nutritional needs that have been discovered. One of the important tasks of teacher education in this field is to help teachers and prospective teachers become aware of and gain skill in developing a wide variety of activities. Only three kinds of activities will be described here.

1) Broadening the range of foods eaten by children. It is difficult to plan balanced diets if the range of foods that children will eat is limited, and unfortunately many children have not learned to like some kinds of foods. Many teachers have been effective in broadening the range of foods that children like and will eat.

A second-grade class in Cincinnati and their teacher (North Avondale Elementary School) grew some greens, radishes and onions in the classroom and on a plot on the school grounds. They used these salad materials to prepare a tossed salad. The children ate the salad with considerable relish. In fact, it has been the experience of many teachers that children are more likely to eat foods if they know 'what it is made of.'

After a visit to a nearby airport, these second-graders constructed a simulated airplane. The airplane was manned by a pilot, copilot and stewardess. A nutritious and tasty lunch was served 'in flight.' Later the children invited their mothers to take a ride on their airplane, and again they served a nutritious lunch. With considerable imagination, this teacher developed a variety of activities to help her children learn to eat new foods.

Do these kinds of experiences make a difference? It is difficult to evaluate the outcomes of such experiences, but the children's parents made some pertinent comments. One boy upon leaving the dinner table had said, "Mother, this was a good dinner." His father asked him why he thought it was a good dinner. He said, "We had all of the different kinds of foods we need." Then he went on to explain what foods are needed by the body. One mother stated that her daughter for the first time was eating and enjoying tossed salads. In some cases at least, these kinds of experiences in elementary schools help to broaden the range of foods that children will eat.

2) Developing an awareness of the need for adequate nutrition. The need for food of some kind is apparent to all, but too few people are aware that 'what we eat makes a difference.'

In a school in New Jersey (Sparta Township Elementary School) a group of sixth-graders kept a record of the foods they ate for breakfast for several days. In many cases their records did not compare very favorably with the foods recommended for an adequate breakfast. They decided to try to find out whether the foods eaten 'make a difference.'

They fed two white rats a diet of fruit, milk and cereal. Two other white rats were given a diet of sweet buns, coffee and a little milk. The youngsters weighed the rats periodically and recorded the weights on a chart and carefully noted the changes in appearance and behavior of the rats. Differences in weight, size and condition of the fur became apparent.

The pupils took the rats and charts to other classes in the school so that younger children could see the changes that had taken place. The rats, posters and graphs were displayed in a conspicuous place so that children could see them on their way to the school cafeteria.

Did the rat feeding demonstration make a difference in the patterns of eating among these youngsters? When asked they commented, "All of the children in our class now eat breakfast before coming to school." "We are eating better breakfasts now, and we are more careful about eating the right kinds and amounts of foods for lunch and dinner." "I have persuaded mother to eat a good breakfast—before our study she only drank a cup of coffee for breakfast." "Our younger brothers and sisters are eating better after seeing what happened to the white rats." A follow-up breakfast survey showed marked improvements in the kinds and amounts of food eaten for breakfast.

Similar animal demonstrations have been conducted in many schools throughout the country. A number of such projects have been exhibited in science fairs (6). These demonstrations have been an effective way of changing habits of eating, and children have become acquainted with the controlled study as an approach to solving problems.

3) Developing a concept of what constitutes an adequate diet. The major aim of nutrition

education, of course, is to help youngsters to eat the foods that they need for good health. To do this they must develop some concept of the kinds and amounts of foods that they need.

In many cases children develop a concept of what they should eat as they make a study of the foods that they actually do eat. They are encouraged to evaluate their patterns of eating. This evaluation is usually done through the use of such resource materials as the *Essentials of an Adequate Diet* (7) and the charts, filmstrips and other teaching materials that have been developed from it. From such materials they can get a concept of what kinds of food they should eat, and they are led to evaluate their patterns with those that are recommended (8).

NUTRITION EDUCATION IN THE CURRICULUM OF THE ELEMENTARY SCHOOL

We have described some practices in nutrition education that seem to have promise. However, there are several problems involved in introducing such practices into the curriculum of the elementary school.

The elementary school curriculum is crowded. Many demands are made on the time and energies of the children, more on the elementary school teacher. In some cases, such fields as nutrition education are not recognized as being in the province of the elementary school. Many elementary school teachers have a very limited background in nutrition education. They have had little opportunity for the study of nutrition as a science and the various possible ways of working with children in nutrition education. Sometimes, the teachers have nutritional problems of their own. These are some of the obstacles that must be overcome in the further development of nutrition education.

Nutrition Education as a Part of Established Areas of the Elementary School Curriculum

In part, the study of nutrition should be developed in subject areas that are already established in the elementary school curriculum. These subject areas are broad and nutrition is an important part of some of them. Certainly the study of nutrition is a part of health education. Here children should have an opportunity to learn the relationship between the foods that we eat, general health, rate of growth and life expectancy.

In science children can study how foods are produced, handled and processed. They learn of the contributions of various foods in the diet and their functions in the body. Arithmetic computations, graphs, charts and studies of food use and waste can be carried out in the study of arithmetic. In the social studies, children learn of the sources of various foods, the problems of food distribution, food habits in other cultures and the contributions that various occupations make in providing us with the foods we need.

The children in their experiences in home and family life education learn how foods are prepared and how eating together contributes to happy family relationships.

Development of Specific Units in Nutrition

Although one of the major routes for the development of nutrition education in the elementary school is through subjects already established in the curriculum, in addition children should have some opportunities for a more concentrated study of foods and nutrition. This will give children greater opportunity for a systematic study of nutrition and to gain some understanding of nutrition as a science. It will give them a better chance to understand why certain foods are essential to health as well as what foods are needed. Unless such experiences are definitely planned for, they will be omitted under the pressure for time and energy in the elementary school.

The number of specific units in nutrition education and their place in the curriculum can and should vary from school to school. One pattern that may have some promise is to plan for at least one definite unit on foods and nutrition in the primary grades, in the intermediate grades, and in the upper elementary or junior high school. In all of these units of study, specific attention should be given to the nutritional needs that are discovered among the youngsters in the nutritional status studies.

In the primary grades, the emphasis should be on widening the range of foods that

children will eat and developing a concept of what foods are needed. In the intermediate grades greater attention is given to evidence that 'what you eat makes a difference' and the functions of various foods in the body. These studies should be reinforced and extended in the upper elementary or junior high school grades.

School Lunch as a Laboratory for Learning

Basically, a laboratory is a place for the testing of ideas. The school lunch can be one of the most effective means for teaching nutrition if it becomes a place where children and teachers can test ideas concerning foods and eating. In the school lunchroom children should have a chance to try out new foods and to practice their learnings in nutrition. Although practice doesn't always make perfect, it usually leads to improvement. Through their contacts and observations in the lunchroom, teachers can evaluate various approaches to the teaching of nutrition and, perhaps, find better ways to change the behavior of children.

For maximum effectiveness there should be activities in the classrooms related to the school lunch program. Children may learn of the origins of various foods that are served in the lunchroom and be led to try the foods of other people as they study other countries and other cultures. They may learn the various ingredients of new and unfamiliar dishes and how they are prepared. These are samples of activities that convert a 'feeding station' into a laboratory for nutrition education.

A NUTRITION EDUCATION PROGRAM IN ACTION

One of the most significant nutrition education programs that we have observed has been carried out since 1948 in the Robert Moton School located on the outskirts of Westminster, Maryland.

The nutrition education program in the Robert Moton School developed from a child study group that was organized among the teachers and administrators. They found that the children were frequently absent from school because of colds and other illnesses. The children were relatively small for their age, tired easily and were generally not very alert. County health authorities diagnosed obvious skin disorders as dietary dermatitis.

The teachers carried out a dietary survey. They found that 38% of the children usually came to school in the morning without having had breakfast; another 38% usually ate breakfasts that were considered inadequate, and only 24% ate adequate breakfasts. Too often for lunch, the children brought only sandwiches filled with sweet jams and jellies rather than meat or eggs. Although they lived in a dairy district, many of the youngsters were not drinking enough milk.

The faculty called upon the homemaking teacher, the county school lunch supervisor and experts from the State Department of Education to help them plan their school lunch program. A Community Nutrition Council composed of representative parents, teachers and a member of the student council was set up to plan over-all policy. This nutrition council sponsored 'pantry showers' where members of the community contributed canned foods and staples. They obtained a deep freezer so that perishable foods could be purchased in large quantities. Through their efforts the price of school lunches was reduced so that children from large families could afford them.

In the school lunchroom, the children and teachers eat together around 'family' tables. A great deal of attention is given to the table manners and social graces that are deemed to be important in life. Often parents, especially fathers, drop in during the lunch hour and eat with their children. The lunchroom is a place where the children can get nutritious food and eat it in a relaxed atmosphere. Committees of children work with school lunch personnel to plan menus.

The work in nutrition was related to the teaching in many other areas. Spelling lists were developed from misspelled words on food records. Arithmetic took on new meaning as the children calculated the cost of food purchased for the school lunch, and compared the costs of various kinds of meals. Social studies classes learned about the different places from which their foods came. The children and their teachers turned to the homemaking teacher for help in meal planning and food preparation, and the

agriculture teacher worked with the pupils on planting and cultivating the school garden.

In the first grade, some youngsters had never visited a dairy farm and knew very little about how the milk that they drank was produced. Fortunately, the father of one of the children operated a modern dairy farm, and the children were invited to visit this farm. Some of the mothers of the children accompanied them on the trip. The children saw the many precautions that are taken to insure clean, safe milk for drinking and they had a chance to ask their innumerable questions about cows and where milk comes from. When they returned to their classroom, they developed experience charts telling the story of their trip.

The second and fourth grades tried to gain a better understanding of the people in the community who help provide food for all. In both cases, this involved writing letters to arrange for visits and thank you notes to those who helped them. The second-graders tried to express some of their ideas about food in the form of poetry.

A number of special activities were carried out in the school and also in the community. Several classes held tasting parties to introduce an unfamiliar food or to develop some appreciation for a disliked food. Once a year the children planned and invited their mothers to a 'Mothers Day Breakfast'. One Parent Teachers Association meeting each year is devoted to a discussion of foods and nutrition. The local ministers cooperate with the program by discussing the moral and ethical aspects of foods and eating in their sermons.

This program, with its emphasis on nutrition education, has been in operation since 1948. Has it made a difference? The teachers and staff say 'yes,' and they point to some concrete evidence. Before this program was started, school attendance averaged about 80%. In the school year 1955–1956, the last year for which records were available, the average school attendance was 91%. An important factor in this improved attendance is that fewer children are remaining home with colds. The health records also show that there are fewer children who are underweight. Has the improved nutrition of the children had anything to do with these improvements?

In 1949, a small percentage of the youngsters participated in the school lunch program and, at that time, most of the children were judged to be lacking in table manners, and in the practice of social graces. Since then, there has been a 60% increase in the participation in the school lunch program, and the teachers have observed that most of the children are very polite and have table manners that might be the envy of many. Also the lunches that are brought from home, in general, now are well-planned and nutritious.

Some of the children who were involved in the program in the first years are now adults living in the community. One of the girls has become the school lunchroom manager. The homemaking teacher visits the homes of each of the children in the school at least once a year. In her opinion, the nutrition work in the school has had an influence on the patterns of eating of families in the community.

This program of nutrition education in the Robert Moton School is continuing. The principal, the homemaking teacher, the school lunch supervisor and several teachers have worked with this program since 1948. In the opinion of the principal, this emphasis on nutrition has resulted in an improvement of teaching in general. New staff members, of course, have not had the benefit of all of this experience. However, all new teachers participate in an orientation week before beginning work in the school. A series of slides and scripts have been developed which tell the story of Nutrition Education in the Robert Moton School. The staff of the Robert Moton School hopes to build on its experience and continue to improve the nutrition education program.

This is an example of what one group of dedicated teachers and administrators has done. The program was based upon the needs of the children that were discovered and studied by the teachers and administrators. It appears that their enthusiasm and imagination in working with children have improved the ways of living in their community. Are there other communities where school teachers, administrators, nurses, doctors and school lunch people should make a similar contribution?

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A Challenge to Professional Education

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THIS IS, INDEED, a challenging question and one that almost frightens me when I think of the task involved in training nutritionists and dietitians. It seems to me that the challenges in the professional education of nutritionists and dietitians today are almost paradoxical in nature. They are, first of all, for deeper specialization in a chosen area and, second, for greater breadth in many areas. In addition we need to train for an understanding in human motivation.

I think all of us would agree that training in nutrition must be soundly based in the sciences of chemistry, biochemistry, physiology and other biological sciences. In planning for this breadth and depth of training the challenge must also be accepted by home economists in general, because most nutritionists and dietitians are trained in the broad area of home economics. Home economists work with the problems of families and the individuals within families. Within this broad field there must necessarily be specialization in one area because the field is so broad that no one person can be a leader in more than one or two areas, at least. The specialist, however, no longer can work in a world in which the mysteries of space impinge at so many points without having an understanding of how the disciplines of history, art, literature and the physical sciences affect one's own specialization. Yet in stressing breadth there is danger—and I think real danger—that there will be a skimming in many fields without a depth of concentration in any area.

As was said before, not only must a nutritionist or a dietitian have an understanding of the world in which he lives and of his own field of specialization, nutrition, but he must understand human motivation and drives. He needs this understanding of people to aid him in bringing about changes in the way people operate—in this case, in the way they eat. He must have an understanding of the social sciences, of psychology, of anthropology, of economics, of sociology and of the principles of education.

Nutrition education has been defined as the retail end of nutrition. This certainly means, as it does in the world of commerce, that the effective person must not only understand the goods he is selling but how to sell them effectively. Certainly this involves understanding the customers and how he can get his ideas across to the customers. That is how he can communicate with and convince the customer of the need to buy or, in this case, to use the idea.

The home economist—and in this case the nutritionist and dietitian who is a home economist—must see himself or herself as one whose primary aim is to improve the lot of families in our own as well as in other cultures. The very essence of improvement is change—change in the deeply-rooted habits of daily life. To cause change, as has been said, is a hard thing to do and involves a real understanding of human motivation.

Gardner Murphy has said, "An integrated personality is one which utilizes effectively and without conflict all that it possesses, indeed, all that is latent within it, whether these qualities be innate or acquired, and whether they be those which happen . . . to be the most prized by the individual and his environment, or the reverse." He has described the good nutritionist, and also the kind of integration the nutritionist hopes to achieve in his 'customers.'

In order to do all of this, the student must first of all get some depth of understanding of himself so his own shortcomings do not stand in his own way. As an illustration of this, I remember when I was working in the elementary schools helping the teachers with nutrition teachings, the teacher whose breakfast project failed completely. I wondered why it did until she finally admitted to me that she, herself, never had liked breakfast and did not eat it. Later she changed her own attitude and a nutrition

project which she was carrying on was so successful that it was chosen to give a demonstration class for a PTA meeting. In other words, she had resolved some of her own feeling so she could now sell the idea of the need for a good breakfast.

As the student learns to understand himself, he also learns more about other people and increases his ability to wonder and to understand why they behave as they do. In my opinion, in order to secure the great values inherent in such a broad education, we know that work beyond the baccalaureate or even the master's degree is becoming necessary. I have found that this idea can be put across even to college freshmen. I so thoroughly agree with Dr. Jacobson that we should begin very young to implant our ideas. As I have worked with the diet of young children for many years, I have become convinced of the advantage of beginning early. I believe and I would like to emphasize that we must begin to implant these ideas of the need for post-baccalaureate professional education as early as the freshman year in college.

In my opinion, some of the questions for those who plan for and supervise the professional education of nutritionists and dietitians are: *1*) How can we make the student care what happens to people? How can we awaken or foster the sense of social responsibility in the young student? I suppose those of you who are involved in the training of students are confronted with this every day, as I have been; *2*) How can we stimulate students and even teachers to really know the needs of individual families and their members while they spend time in deep concentration in the subject of nutrition. The greatest danger here, I believe, is that teachers lose contact with real situations and so they cannot or do not teach with a sense of reality. Often they do not even realize when they are out of touch with real families. One cannot learn and become competent if situations are divorced from realities. Nutrition can not be taught successfully in a vacuum. We can make our teaching so real that the principles can be applied to a real family living in the slums of a great city or in a developing country; *3*) As many of you will remember, Toynbee has said that "our age will be remembered not so much for great scientific discoveries and inventions but because it is the first age since the dawn of history in which mankind has dared to believe it practicable to make the benefits of civilization available to the whole human race." If he has truly spoken wisely—and I hope you agree with me that he has—those who are in the field of nutrition are heavily involved in this great process.

Any of these challenges are so great that any nutritionist knows he cannot do it alone, even in a small way. Nutritionists and dietitians are being driven, and fortunately so I believe, to the need to work together closely with others whose competencies supplement their own. Perhaps the phrase 'teamwork' has been used too often but the idea behind the phrase has not been exploited nearly enough. If we believe in this approach, we must so structure our educational programs that students will gain an understanding of the importance of working with others, of respecting their ideas and of constantly learning from them. We must train the student to become highly competent in his own area but, at the same time, to recognize his own limitations and to seek the assistance of people who have other competencies.

Students do not just fall into these ways, and the education of nutritionists and dietitians will not just happen by lucky chance. Those who shape the educational programs of the future must set the stage. First, the true goals must be carefully thought out and then a structure for learning, and for developing understandings must be set up.

I should like again to emphasize the three goals which seem to me to be of great importance: first, to promote deeper training than we have now in the area of nutrition, with more emphasis on basic sciences and more and greater understanding in the scientific aspects so that the student comes out with real professional competence as well as with an understanding of the important role nutrition can play in the lives of people; second, to assist the student to pursue study in the other areas in order that he begins to understand the world in which he lives—such a student would truly be broadly educated; third, to foster in the student a desire to understand human beings and why they behave as they do; also, to understand how and why changes in behavior take place.

Along with all of this, I believe we should consciously instill in students the idea that the years in school, the years of formal training, are only the beginning of an education in nutrition.

Nutrition Education in Schools of Medicine and Public Health

F. J. STARE

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ABOUT TEN YEARS AGO I prepared a paper entitled "Teaching Nutrition to Medical Students" (1) and a second paper entitled "Training Physicians in Public Health Nutrition" (2). The former resulted from a report of a committee appointed by the Dean of the Harvard Medical School to make recommendations on the teaching of nutrition to medical students and the latter from a report of a committee of the Nutrition Section of the National Health Assembly. Both of these papers were quite specific, spelling out in 1–2–3 fashion the subject material we thought should be presented, how it might be presented, and how one might seek permission of the curriculum committee and the Dean to present it. As far as I am concerned, the principles presented in these papers still stand.

Nutrition is such a broad and important subject in health that all physicians should have some awareness of the subject. Professional training in nutrition for the physician is important and should include some or all of the following: *a*) basic and historical information on the science of nutrition, in perspective to the other sciences; *b*) applications of nutrition to medical and health problems; *c*) an account of recent research in nutrition as it applies to medicine and public health with some evaluation of present and future problems; *d*) the economic, social and psychologic aspects of nutrition.

Professional training in nutrition should be given by each of the following general procedures: *a*) instruction in nutrition should be included in each of the years of medical education; *b*) most, but not all, of this instruction should be incorporated in standard courses of the curriculum; *c*) special courses in various phases of nutrition should be available for those students desiring to know more about nutrition.

The same general principles apply to students in Schools of Public Health except that usually these students are older, they have been out of medical or nursing school for variable periods and usually have forgotten what little they learned about nutrition in whatever science courses they may have had. Thus special courses are needed to teach the basic principles of modern nutrition in Schools of Public Health, for without an accurate understanding of principles and facts it is a little hard to have intelligent application. This applies only to those who are nutritionists. The administrative personnel in public health must learn the many ways that modern nutrition enters into public health problems and what they can expect from a trained nutritionist.

Three years ago, Dr. Theodore B. Van Itallie, who was then in our department, and I prepared a paper entitled "Nutrition and the Curriculum" (3). Much of what I have to say is taken from that paper. We pointed out that the teaching of nutrition to students in the health sciences, namely, medicine, dental medicine, and public health, should still be a matter of concern to educators in these fields. Although interest in this problem undoubtedly reflects awareness of the increasing importance of nutrition in medicine and related fields, the lack of action suggests that there remains considerable uncertainty about the place nutrition should occupy in the curriculum.

Much of the uncertainty about nutrition appears to have resulted from lack of a clear conception of what is encompassed by the term 'nutrition', and of the precise relevance of this subject to the health professions. In a

way, it is not surprising that such an indeterminate picture has evolved; nutrition as a subject is not readily categorized.

A useful way of approaching the problem of characterizing nutrition is to examine its orientation. Just as microbiology has principally to do with microorganisms, particularly as they affect health, so is nutrition concerned with food and its constituents the nutrients —water, protein, fat, carbohydrate, vitamins and minerals—as they relate to health. Thus, all considerations which are relevant to nutrients are, by extension, relevant to nutrition.

Because of its orientation to the nutrients in a very broad sense, the territory of nutrition seems on casual inspection to be almost limitless. However, this is only an appearance. If a distinction is made between the core of nutrition and its many ramifications, the subject becomes wieldable.

Like other sciences, nutrition can be divided into two general areas, 'basic' nutrition and 'applied' nutrition. Basic nutrition is concerned primarily with the metabolic facts of nutrition and constitutes the core of the subject; applied nutrition has to do with the use of nutritional knowledge in dietetics, medicine, dental medicine and public health.

For some reason the identity of basic nutrition has remained obscure. While everyone knows that a bacteriologist is not necessarily a clinician, no satisfactory term exists to distinguish the investigator doing nutritional research from the public health nutritionist whose main job deals with certain concepts of applied nutrition. Both may be called nutritionists. It does not seem to be generally appreciated that there is a body of knowledge about nutrition which can be readily identified as its foundation and upon which are based many of the principles which guide the practice of nutrition. Thus, while the distinction between the basic and applied aspects of most other sciences appears to have been clearly defined, this has not been the case in nutrition. Nutrition has not yet found a home among the basic medical sciences.

When we consider the basic sciences which the medical and dental curriculums share, it is immediately evident that such subjects as biochemistry, bacteriology, pharmacology and physiology—to mention a few—all have important nutritional aspects. For example, nutrition and biochemistry are so intimately related that it is frequently difficult to distinguish one from the other. The nutritional characteristics of bacteria are of enormous interest to microbiologists; nutritional disorders form a significant fraction of the subject matter of pathology; pharmacology textbooks contain extensive discussions about the use of vitamins, other nutrients, and antinutrients in therapeutics. Recital of the many relationships between nutrition and the basic medical sciences could be an endless affair.

In the clinical subjects it is much the same story. One cannot discuss such subjects as diabetes, atherosclerosis or liver disease without becoming involved in nutritional considerations.

In the clinic a problem involving treatment of a cardiac arrhythmia has a potential continuity with physiology and pharmacology; on the other hand, a far more common clinical problem, the prevention of coronary thrombosis or a difficult problem in parenteral nutrition, cannot be related to any preclinical discussions since sufficient basic nutrition usually is not effectively taught as a formal preclinical subject.

A misconception that exists among many who guide the educational destinies of our medical and health schools should be examined. Because of the wide publicity which vitamins have received and because of the dramatic nature of full-blown scurvy, beriberi, pellagra and rickets, nutrition has become identified in the minds of many physicians and health leaders primarily with the classic deficiency states—states which have largely disappeared from this country.

We all know that much more is involved, but it has not been sufficiently appreciated that nutrition is concerned with atherosclerosis, obesity, hypertension, liver disease, problems of supportive care and a list of other disorders too long to mention.

In thinking about nutrition and its relationship to medicine, it is useful to distinguish between disorders in which the nutritional environment (usually the diet) is at fault, and disorders in which the environment is not at fault, but the individual becomes

malnourished because of a disease which prevents nutrients from getting to the cells in effective amounts. This second type of malnutrition is often called 'conditional malnutrition.'

Upon reflection it will be realized that any disorder which interferes with the ingestion, digestion, assimilation, transport, storage, utilization, or excretion of a nutrient may be responsible for a form of conditioned malnutrition. Since a disordered state of nutrition occurs to a varying degree in almost all forms of disease, the importance of nutrition in medicine and public health would be difficult to exaggerate.

The November issue of the *Journal of Medical Education* contains a paper by Dr. Edward High of Meharry Medical College entitled "A Survey of the Teaching of Nutrition in Medical Schools" (4). This is based upon questionnaires obtained from sixty medical schools representing twenty-nine states and the District of Columbia, a response, incidentally, of 91% of the questionnaires sent out.

Although the majority of the persons answering the questionnaire felt that nutrition should be taught in an integrated manner, many expressed the urgent need for better training of the students in the basic fundamentals of the field by giving such information in a special course.

Dr. High points out that although need for nutrition teaching in the standard medical curriculum is recognized, his survey revealed that in many instances very little attention is directed to organization and coordination of nutrition teaching.

In conclusion, I have attempted to indicate that some of the uncertainty which exists about the position of nutrition in the curriculums of medical and health schools results from the indeterminate picture most educators in the health sciences have of nutrition and of the misconception that since the classic vitamin deficiency diseases have largely disappeared in this country, why then bother much with nutrition.

When nutrition is considered in terms of its orientation to the nutrients, the vast territory it covers becomes evident; however, the subject is less unwieldy if it is divided into basic nutrition and applied nutrition. It has not been generally recognized that a body of basic nutritional knowledge can be identified which is distinct, particularly in its emphasis and organization, from the nutritional information taught in biochemistry and physiology. Thus the important nutritional problems that arise in the clinic are not dealt with in terms of principles derived from knowledge of nutritional fundamentals.

Lastly, since most clinical and public health subjects are so permeated with nutritional considerations, it would appear that a more effective application of the principles of modern nutrition would result in better supportive care of patients, a more enlightened understanding of causation of disease and, hence, the possibilities of a certain amount of prevention, and a marked improvement in general public health.

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Summary

E. NEIGE TODHUNTER

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I HOPE THAT you have been stimulated by these presentations of the importance of nutrition information and nutrition education at so many levels. I think Shakespeare has the answer for us, as he has had on so many occasions. Shakespeare is a rich source of information about medicine and he has many fascinating things to say about nutrition. I am not quoting him correctly at the moment because I am doing this from memory, but I think it goes something like this: "If we knew what it were good to do, cottages would be palaces and beggars would be kings."

I hope we know what were good to do. I hope you agree that if we could get sound teaching in basic nutrition in the medical schools, if we could do a more effective job of thorough training in the basic science of nutrition and the applications of nutrition in our colleges and universities where we train dietitians and home economists, if we could get more effective nutrition information throughout all the elementary school programs and throughout our general sources of information that reach to the public, those are the things that were good to do.

The difficulty is that it is not easy to do. This is a field where we all tend to pay lip service. We say, "Yes, it ought to be done," and then we go back into the laboratory with the test tubes or beautiful apparatus or animals that stay put and do what we want them to do, and we go on in the same pathways that we were following. But we do take care of our own education, through groups such as this, through reading our research journals, going to the annual meetings of professional organizations, and attending conferences; and we gladly seize the opportunity to come to symposia such as this. We take care of our own education but what are we trying to do for the education of others who we know would profit to a very large extent if we could put into effect or make function what we know about nutrition today? We know that nutrition affects the life, health, and well-being, in fact, everything about people except some types of red hair!

We have put the funds and energy into developing the science of nutrition, and the progress has been great in the remarkably short time, comparatively speaking, that we have been working in this field. But research in nutrition is just half the job. I might use the analogy—I may use it wrongly through ignorance but I will try—that we are like the rocket that does not reach its goal unless it goes into the third stage, and the third stage, as I see it, is nutrition education. We are using the first, and possibly the second stages of our nutrition science, but we are not going to be effective until we can reach all people in this country as well as in other countries, with this knowledge.

Possibly we need to do much more research in the methods of nutrition education. We do not know enough about how to reach people, how to motivate people, or how to bring about change in practices.

Along with the need for more research in this area of nutrition education, I think we need to consider very carefully that challenge that Miss Beeuwkes has thrown out to us. The challenge of the proposal for a Nutrition Education Foundation, where we would have not competition between groups, institutions, or manufacturers, or any others—not competition but cooperation. This is a proposal to use the combined efforts of all groups of educators, of scientists in every field and in industry, working together to provide reliable information to people about nutrition. This could be a hub of nutrition, as it were, from which would radiate the

effective ways, means and knowledge to reach people at all levels.

I think that at times we have been a little afraid that we didn't have an exciting or a stimulating story to tell people when we talk about nutrition. We do have as fascinating, if not a more fascinating, story than any that can be told in any field of science, one that is a challenge to young people today, one that we know is an epoch of adventure, a story of research and of great discoveries. Nutrition permeates all phases of history of our people, whether on land or on sea or in the air. It has influenced history. We find it all through literature. You find foods and nutrition illustrated in the great arts and in paintings and everywhere.

We have the resources to draw on. We have a story that is exciting and challenging and we need to stand up and make known, wherever we are in whatever field we work, this story of the science of nutrition and what it can accomplish in the lives of people.

We can succeed in nutrition education if we build soundly and squarely on facts. We should get away from that old idea that you have to eat this or that in order to have a 'nutritious'—hateful word—meal; we need to let people know that there are choices that can be made in food selection, that there is a wide variety of foods to choose from, and that we are not taking the enjoyment out of life in talking nutrition education. We should let people see that we are putting the real enjoyment into life.

If we will put these thoughts and suggestions, along with the very wonderful presentations that were given to us by the four speakers this afternoon—if we would put these into action, I think we could see a real change in the health, well-being and attitudes and enjoyment of life of our people.

Closing Remarks

C. L. RUMBERGER

H. J. Heinz Company

AT THE CLOSE OF this Symposium I would like to add my thanks to the speakers who have done such excellent work in presenting up-to-date material. I would like especially to recognize Dr. King, our Honorary Chairman. Through his excellent cooperation and counsel the original organization of the Symposium was planned. He has been in attendance at every session and I know he has been intensely interested in the subjects discussed and in meeting this tremendous number of people who were vitally interested in the broad aspect of the nutrition field.

I am sure you are all well acquainted with Dr. Burton by this time. Every meeting must have a workhorse—or we might better call him the pilot of the Symposium. Dr. Burton has spent a great many hours in the past 5 or 6 months developing the details of this meeting, and I want to give him recognition at this time so that you will all fully understand what he has meant to the success of this conference.

This afternoon it is planned for you to visit our new research center. You will find that this is not a large building, but we believe it will be a very efficient structure for the work which we intend to do. The building was constructed with approximately 20% expansion possibility. The general philosophy of our organization in Research and Quality Control work is based around the thought of not more personnel, but better trained personnel. We have reached the conclusion that once a research program has been decided upon we can then determine the extent to which we can successfully do the research work with our own organization. If, in laying our plans, we believe we can contract with other research laboratories to do a more successful job on a project, it will be our plan to use these specially trained groups as a supplement to our own operations. Our present division is made up of 155 people with over 60% of them university, technically trained people.

The dedication of this new Research Center has given us the vehicle for organizing and scheduling this 2-day Nutrition Symposium. We hope that you will enjoy your visit to our new Research Center.

DINNER ADDRESSES

Reflections

H. J. HEINZ II

H. J. Heinz Company

AS THE HOST and toastmaster this evening, I would like to express the sincere hope that you had an enjoyable day wandering through the new Research Center of which, I confess, we are a little proud, and I know, from what so many of you have said so sincerely, that you share some of that feeling. I am very touched and grateful, as are my colleagues, that you have enjoyed one another's speeches, even though you have not always been able to answer back in the public forum.

Tonight's dinner concludes the program of our Symposium and I hope that you share my feeling that this conference, this presentation of observations and give-and-take of stimulating ideas, has been a constructive contribution to the science of nutrition. With the memory of the various presentations still fresh in our minds, I wish to thank all the participants in the program for the part they have played. This includes the speakers who have so ably enriched our knowledge, the Symposium Chairman—Dr. King—and you, honored guests, many of whom have traveled great distances to be with us, as well as the others whose behind-the-scenes activities during the last two days and during weeks of advance preparation have made the Symposium possible.

Yesterday, when I welcomed you, I mentioned that we had entertained the thought of such a conference for a long time and that the plans for this Symposium crystallized when an appropriate occasion—the opening of our new Research Center—presented itself. Some time ago we made plans for another, perhaps more lasting contribution to the field of knowledge of human nutrition. Again the time has come to translate thought into action, and since the spring of this year we have been actively engaged in this enterprise.

Many of you are familiar with our booklet, *Nutritional Data*. It had its beginnings in 1934 when we published a brochure of descriptive and tabular information relating to the nutritive value of foods—for the guidance of physicians, nutritionists and public health workers. What began modestly as *Nutritional Charts* is now, 15 editions later, a much expanded work, and possibly the most gratifying token of acceptance has been its adoption as a teaching aid by a majority of medical schools in this country. However, the scope of our *Nutritional Data* book has been limited, perforce, by its format.

For some time, we have been envisioning the publication of a complete handbook of nutrition—a definitive treatise which would condense and encompass the entire field of human nutrition, both in health and in disease, in a concise and authoritative manner. One of the purposes of this handbook would be to serve the physician as an over-all ready reference book on nutritional matters. It is hoped, however, that it would not only be a practical addition to the armamentarium of the practicing physician, but also a reference book for hospital dietitians and nutritionists, and a text for teachers and students of nutrition, medicine, nursing and home economics.

Such a book—the *Heinz Handbook of Nutrition*—is now being written by Dr. Benjamin Burton of our research staff, with the assistance of a very distinguished advisory board of editors. You have met some of them during the Symposium and they are recognized authorities in their respective fields of study, both in nutrition and in

medicine. They are: Dr. Floyd Daft of the National Institutes of Health, Dr. Grace Goldsmith of Tulane University Medical School, Dr. Helen Hunscher of the Home Economics Department at Western Reserve University, Dr. Henry Sebrell of the Columbia University Institute of Nutrition Sciences, Dr. Fred Stare of Harvard University, and Dr. Glen King, the chairman of this advisory group.

We envision this book as a living contribution which will be revised and brought up to date periodically to keep abreast of the latest advances in the many fields which it encompasses. We hope that it will become an accepted, authoritative reference book and that eventually it may even become a teaching aid in schools of medicine and nursing and in university departments of nutrition and home economics.

A word about what has taken place here during the last two days. I cannot help but liken it to a wonderful, spontaneous chemical reaction—sincere people from the academic world of science, practicing physicians and nutritionists, educators, and men of industry devoting themselves selflessly to interrelated problems of mutual interest, which affect not only the people of this country but the people of the world. It is a thrilling experience to find all of us lit—if you please—by the same enthusiasm and fire.

At this point I would like to add a word or two about our honored guest of the evening, Dr. Milton Eisenhower. If I attempted to elaborate on the background and achievements of our main speaker for tonight, I would only be repeating what so many of you know. Suffice it to say that he has brought deserved and independent distinction to his name in the face of heavy competition. A more varied career is hard to find. Milton Stover Eisenhower has been a newspaper editor and professor of journalism, a vice consul and an Assistant Secretary of Agriculture, director of information of the U. S. Department of Agriculture and its land use coordinator, director of the War Relocation Authority, and a distinguished university president at three major universities, Kansas, Penn State, and now Johns Hopkins.

His role as humanitarian on the Famine Emergency Relief Committee and on the executive board of UNESCO is as well known as his efforts to improve the educational system of the nation, or his role as Special Ambassador and Personal Representative of the President to Latin American countries. It is in this last role, which he has practiced now since 1953—having really been a specialist and a continuing observer and reporter of events and situations in some 17 of the 20 Latin American countries—that he brings us a message for this evening. It is therefore most appropriate that since our interests in nutrition and its attendant problems go back to agriculture and forward into the standards of living in which we are interested, that Dr. Eisenhower speaks to us of Latin America and the general problems of nutrition science.

The Outlook in Nutrition

C. GLEN KING

The Nutrition Foundation, Inc.

AS A MEMBER of the faculty at Columbia University, I like to use the term, President Eisenhower. During the heat of the national election campaign before the brother of our honored guest this evening became President of the United States, we at Columbia could refer to 'President Eisenhower' in proudest, confident terms, and no one could say us nay. They couldn't accuse us of being politically partisan or biased at all, but we were just as happy as could be to see the election an accomplished fact.

The guests at this conference have been looking forward with enthusiasm, I am sure, to the privilege of hearing an address from the highly honored President Eisenhower of the Johns Hopkins University.

Mr. Heinz has been very generous in his introductions of me during these meetings. I had thought his suggestion that I might help in setting up the program as an assistant to Dr. Burton was a coincidence arising from the fact that Mr. Heinz was elected President of the Nutrition Foundation in the year that we had reached a total of 57 member companies and—believe it or not, he had the patience and good grace not to say anything about this famous number until I reminded him of it.

One point that has stood out boldly and commendably during this conference has been the forthright challenging of too much complacency about what we know or don't know about nutrition. I like to see the top authorities in the United States and in other parts of the world stand up and frankly admit the limitations in what they know. For example, a human infant is probably very well nourished by normal human mother's milk. That is actually a fundamental challenge in our sophisticated modern life, when the ideas supporting popular trends in infant feeding are open to honest doubts. I think we should look at many other aspects of currently accepted food practices just as critically as has been evident in this instance.

The next step was to challenge whether or not our current practices are subject to improvement beyond the stage of feeding infants. Our criteria should be based on long-range regard for the consumer—not what is easiest for a food manufacturer, not what is most convenient for the mother, not what is simplest for the family doctor—but what is best for society as a whole.

In the Foundation we approach all of our work in that spirit and I have been gratified to find that the food industry has been willing to support regularly through the years since 1942, fundamental research and education in our best university and medical centers on that basis. It has been a pleasure to serve with these executives of the food industry, of which Mr. Heinz is one of the outstanding leaders.

I hope everyone noted during the course of the program that the problems in infant feeding cited for research and education here in the United States are also fundamental to further progress in other parts of the world. This is true even though at first glance the detailed conditions appear to be reversed. For about one-half of the world's population, the struggle is a bitter one to find how to feed infants with sufficient good quality protein to maintain life and normal development. In many local areas, the post-weaning death rate, as cited by competent authority may reach levels twenty to forty times the comparable death rate here—i.e. in the age range 1–4 years. In contrast, our discussions here dealt chiefly with the question of whether we have a tendency to feed too much good quality protein to non-breast-fed infants. The fundamental problem is—how much protein of known quality is optimum for a child?

We also find that our life span has reached approximately twice the value that is still experienced in many communities, and that our problems are now related most cogently to fat metabolism and the hazards that are associated with consuming an excess of calories. Atherosclerosis, heart disease, cerebral accidents, diabetes and related breaks in health are dominant aspects of public health. We need information about how fats are formed and utilized in the human body. Only when we understand normal changes more clearly will we be in a position to identify and prevent the changes that lead to breaks in health. The underprivileged nations of the world are more interested in the hazards of too little fat and too little protein for their population in all age brackets. We, as well as they, need to know the approximate margins of safety, below or above an optimum intake.

Fortunately our next speaker is president of an institution where scientists have a notable record in getting the kind of basic information that will give us the kind of answers we need in the long run to solve practical problems in all parts of the world.

It is a pleasure and an honor to present to our guests, the President of Johns Hopkins University, Milton S. Eisenhower.

United States–Latin American Relations

MILTON S. EISENHOWER

President, The Johns Hopkins University

I MUST SAY it was a unique and satisfying experience to be referred to once again as 'President' Eisenhower. This was a title that I somewhat modestly enjoyed in the universities where I served from 1943 to 1953. Then it seemed to be plagiarism and I dropped it. I thought I had a prior right to it—but there are forces bigger than the individual.

My predicament in this regard was dramatically brought home to me by my wonderful 83-year-old father-in-law. We went up to the lakes of Wisconsin for a little rest, and we were, just the two of us, in a boat one afternoon when he suddenly said to me, "You know, Milton, when you first married Helen, people referred to you as my son-in-law; but as time went on they began referring to me as your father-in-law, and I didn't like it."

I said, "Well, Dad, I fully understand because the cross I bear in this regard is much greater than yours."

"No, it isn't, Milton," he said, "because people now call me the father-in-law of the President's brother."

When Mr. Heinz, some time ago, was kind enough to fly over and visit us at Johns Hopkins and asked me to be with you tonight, he knew full well that there was no way in which I could add to your enlightenment in your field of specialization. He was, therefore, good enough to say that after two days of intensive discussion in your professional fields, you might welcome an opportunity to escape and come into one of mine. This is what we are going to do.

I am not sure that these two areas are as far apart as might seem at first glance. I think this will become evident as I go on to speak of some aspects of our relations with the 20 republics of Latin America.

Latin America is a continent in transition. Due to modern communication, its millions of people, like their leaders, have come to realize that poverty, malnutrition, disease, premature death, illiteracy and other blights on human welfare, are neither universal nor inevitable. They realize that some parts of the world have made much greater progress than they have with respect to these great human problems. They are, therefore, unanimously anxious to solve their problems—and to solve them quickly. It is a perfectly natural reaction for them to look to the United States for assistance. If neither the assistance nor the progress is as abundant or as rapid as they would like, the result often is disappointment, disillusionment and sometimes frustration.

They do want to overcome illiteracy, which in some countries is as high as 90%. They do want to throw off the old feudalistic systems that still exist today in a few places. They are making amazing progress with the limited resources at their command in solving age-old problems of disease—such as yaws and malaria—and in some countries their success has been spectacular.

They want to improve their educational systems at all levels—to the highest creative level of scholarly study. Above all, they want to lift the level of economic well-being of all their people.

If for no other reason than a humanitarian one, we of the United States would be forced to take an interest in their problems and to do what we can to help, within our economic and technical ability. I think that our cooperation can also be justified in terms of our own self-interest.

Latin America and the United States are indispensable to one another. Economically, we have a tremendous interdependence: the two-way cash trade today between Latin America and the United States is greater than that with Europe, and vaster and more important than all the trade that we have

with the Middle East, Southeast Asia and Oceania combined. Last year trade with Latin America was about $8 billion—$4 billion each way, and this level of trade is only a fraction of what it can be, in my judgment, under intelligent planning and the proper policies. Our investment in Latin America, now totaling about $10 billion, is higher than in any area except Canada. About 80% of this investment is private, 20% public. On the whole, it earns a fair return.

Politically, the area is certainly of vital importance to us, and we to them. The people of Latin America draw their basic philosophic ideas from the same source we do and, therefore, they believe as we do in human dignity, mutuality in human relations, consecrated intelligence, freedom and independence. Just as much as we do, they want to make progress in a world characterized by peace with justice.

These common aspirations have led in this hemisphere to the development of the Treaty of Rio de Janeiro of 1947 which was the first effective treaty of mutual security in the world. It was later copied by other areas. It led to the Organization of American States, which is the most effective regional organization in the world; OAS has been particularly successful in the political area but in these recent years it has become active also in the economic, social and technical areas—including the peaceful application of atomic energy.

To comprehend the mutuality of political interest among the nations of this hemisphere, all one needs to do is to watch the votes in the United Nations and in the other international organizations. You will find that with only rare exceptions the 20 republics of Latin America and the United States are standing side by side in basic principles and in effective vote.

Culturally, our relations are becoming closer. Considering the waves of migration that moved from most of the countries of Europe, principally from Spain and Portugal, to Latin America, it is not surprising that their preponderant cultural attachment has been to Europe. However, in the last 30 years this has been changed. Today 75% of all of their students who go abroad for study, at the secondary, collegiate, university and even the postdoctoral levels, have come to the United States. English has become the second language of the people; indeed, an American traveler is often embarrassed in talking to laborers or taxi-drivers—and certainly to University students—to find that their English is far superior to one's own Spanish.

Throughout these countries the bi-national institutes do a wonderful job. They are largely self-supporting enterprises, with a modicum of help from the United States. In these institutes, thousands upon thousands of persons are learning English. They not only learn elementary English but also develop sufficient proficiency to read our literature and our history. Thus they learn a great deal about us.

The importance of this cultural affinity, I think, is this: it seems to me that all effective human cooperation, wherever it exists, is dependent upon genuine human understanding, not only among governments but among the masses of the people. Obviously, understanding in and of itself will not yield us the kind of world we want. But neither will there be a successfully cooperative world without understanding. It is a beginning point.

Now, despite our interdependence in the economic, political and cultural fields, there is not today the degree of understanding among the peoples of these 21 republics that there should be to let us achieve the fruitful cooperation we desperately need. In this regard, I think our failing in the United States is greater than that of the Latin American people.

I doubt if many Americans would be so ill-informed as to ask, as one gentleman did of me just before I made my last fact-finding trip to Latin America, "What is the capital of Latin America?" But I think this can be said truthfully: that while the American people have an emotional desire to be good neighbors and good friends and we want the Latin Americans to like us and be good neighbors of ours, we actually know little about them—their motivations, their culture, their history, their problems and their aspirations. Our newspapers carry practically no real news from Latin America. Of

course if there is a revolution, we can find a top headline in our newspapers but the news stories do not explain the circumstances and shifting events that may have led to the revolution.

It is unfortunate, I think, that we have become conditioned to having our news media concentrate almost exclusively on the crisis areas of the world. It is only by dint of careful study and extensive reading that one can become aware of the context in which national and international events transpire. This is especially true with respect to Latin America. I doubt that very many of us, from reading our newspapers, can learn much about the heroic efforts to overcome illiteracy and to raise the living standards of the people whose income may be less than $100 a year. One does not often read of the valiant and effective fight waged by the market women against Communism, and only recently has the surging spirit for democracy throughout the hemisphere become noted. By reporting only highly dramatic events drawn out of context news reports play upon our limited preconceptions—and thus they are doubly misleading.

Latin Americans know more about us than we know about them. This is so for a number of reasons. Nearly all their foreign news comes to them through our press associations, and it is carried in their newspapers and on their radio and television stations. The preponderance of their travel is to or through this country. Further, since they are so dependent on the economy of the United States, they follow the doings of our Congress and our Administration in careful detail. Again, a traveler may be embarrassed to find that the educated Latin is more familiar than he is with the details of a bill pending before our Senate, or with a tariff decision, or with other matters of concern to them.

But this understanding is not enough. It is my sincere belief, after working in this area for a good many years, that there exist today in Latin America serious misunderstandings of the United States in the very areas in which substantive problems exist. Therefore, these misunderstandings stand as serious deterrents to the resolution of problems that very much need to be solved.

In this brief visit with you tonight, I can of course touch only a few highlights.

In all of the Latin American countries, among the highly educated as well as among the less well informed, there is a strong feeling that we of the United States do not consider Latin America to be as important to our welfare as are other areas of the world. Nothing could be further from the truth, but I think we need to consider why they feel as they do. There are two reasons: one, historic, has considerable truth in it; the other, more current, is not founded on fact.

The historic fact is that from the beginning of our development as a nation—and especially beginning with the Monroe Doctrine, which was a useful but nonetheless a unilateral 'Big Brother' policy—the United States maintained a patronizing attitude toward Latin America. We often were guilty of intervention in their internal affairs. On occasions we were even guilty of outright imperialism. These policies were reversed at Montevideo in 1933. The new policy of nonintervention, mutual respect and the recognition of juridical equality of states has been scrupulously adhered to now for 25 years, but memories linger. Even among the most sophisticated people of Latin America a nervous misgiving still remains that, should a crisis occur, we would be willing to violate their sovereignty.

Within this framework, they have watched with amazement our expenditure of billions of dollars in Europe under the Marshall Plan and now more billions under the Mutual Security Act in other areas of the world. These are programs in which Latin American nations have had practically no participation. They have witnessed these vast expenditures at the very time when they could not receive credit in the volume they desired to meet their aspirations. Therefore, against the historic background and the modern fact, they have concluded that we think other areas of the world are more important to our future than they.

Now, they are mistaken about this. One needs to point out that our expenditure of billions of dollars under the Marshall Plan was designed primarily to rebuild productive resources destroyed by war. While these resources were being destroyed, Latin Amer-

ica's trade with us multiplied six-fold, reaching a high level which is maintained to this very day. Further, in restoring Europe both as a buying and selling market, we benefited Latin America almost as much as we benefited ourselves, because a good share of their trade is with Europe. They would not have had this added European trade without the expenditure of the Marshall dollars.

Further, with respect to the Mutual Security Program, these billions obviously are spent not just for ourselves but in defense of freedom wherever it may be threatened, and in this sense those dollars benefit the Latin Americans the same as they do us. In a serious conversation Latin Americans will acknowledge this. But it is easily forgotten and so it is necessary to say this again and again in an effort to eliminate false impressions.

There is a second misunderstanding in the economic area, closely related to the first. Latin America believes, on the whole, that our economic resources are essentially unlimited and that therefore their failure to get public and private capital in the volume they obviously need to make economic progress is due to sheer perversity on our part. I will never forget how surprised a sophisticated government Minister of one Latin American country was when I told him about the burdens carried by the American people. I pointed out to him that our income taxes are graduated very sharply to 92%; that our corporation taxes are 52%; that we are one of the few countries in the world with a capital gains tax; that we have many other kinds of taxes—estate taxes, sales taxes, transfer taxes, real estate taxes. I explained that more than one-third of our total national income today goes into public enterprise, and reminded him that despite the most burdensome taxation carried by any people in the world, we face a Federal deficit of $12 billion which is an inflationary threat—a threat, therefore, to our economy. Nothing could hurt Latin America or any other part of this world so much as the collapse of the American economy.

Well, this very intelligent and sophisticated Latin leader told me he was astonished, and said it wouldn't be politically possible for his government to levy this heavy taxation even on their very well-to-do people in order to get public funds to carry on publicly-financed enterprises.

But then, to pursue the argument, he said that what I was saying was really not relevant to the problem because they only wanted loans, not grants.

This brings up another fact that a good many people of the world don't seem to understand: all of the funds for loans made by the Export-Import Bank and the Development Loan Fund come from the United States Treasury; therefore, such funds have to be obtained from our taxpayers before they can be loaned to citizens or governments abroad.

There is a third serious misunderstanding, still in the economic area. It seems incredible that this should be so but most people in Latin America believe that we fix prices, always to their detriment. Wherever one goes, whether he is talking to university teachers or students or industrial leaders, it will be said, "We have to sell to you at prices you are willing to pay and then we have to buy from you at prices you fix."

You see, they sell to us largely raw agricultural commodities and minerals. The prices of these commodities on the world markets are subject to wide fluctuation. They buy from us largely industrial products—from toothbrushes to automobiles, whose prices on the markets of the world are much more inflexible. This has been accentuated recently because during our recession we have had a situation, almost unique, I think, in economic history: during the recession industrial prices continued to rise; but because of our reduced purchasing, raw commodity prices went down. Therefore, the relationship of free market prices to administered prices became worse, and Latin America suffered. Of course, one needs to point out that all these prices are determined competitively—as they should be—in the markets of the world. The United States Government, of course, has nothing to do, save in wartime, with fixing them.

Another misunderstanding worthy of mention at this point is in the political area. It is one that, I am convinced, is being cleverly fostered by Communist leaders. Wherever Vice President Nixon went earlier

this year and I went this summer, we heard it said that we support Latin American dictators. For us actually to do so would be incomprehensible to them because they recognize that we adhere to the basic principles of democracy in our country; and they ask why, therefore, do we seem to have one code of ethics or principles for ourselves and a different one for others?

I can understand how they might feel this way, but of course such an idea is based on superficial thinking and a completely false impression of the actual situation. I would refer again to the meeting in Montevideo, Uruguay, in 1933, when we reversed our previous policies and agreed thenceforth to adhere to the policy of mutual respect, juridical equality of states, and nonintervention in the internal affairs of other nations.

Now, you can't have it both ways. You can't refrain from intervening in internal affairs and at the same time express moral judgments with respect to the degree of democracy or dictatorship certain nations may have.

Obviously, this whole thing has placed us in a dilemma. In 1946 and 1947 we thought we saw a way out of it, because the Foreign Minister of Uruguay, in an international meeting of the 21 American republics, proposed that since we all agree to the policy of non-intervention, and no nation dared therefore to express this moral judgment unilaterally, the nations collectively should do so and agree to withhold recognition from any country which had a dictatorship. The United States supported the proposal. It was defeated by the Latin American nations themselves by more than two to one.

Finally, on this matter of policy toward dictatorships, it may be said that 'the proof is in the pudding.' There are only one-third as many dictators in Latin America today as there were in 1933.

I leave it to others to argue whether our previous policies had angered the people of some Latin American countries and thus drove them to support ultra-nationalist and dictatorially inclined leaders. I say only that we are now doing our best to let it be known that we do not have friendly feelings for dictators and we do want to take all reasonable steps to encourage the democratic spirit which is abroad and growing in the hemisphere. We will not intervene in their domestic affairs, but we applaud and support the efforts of the Latin American people to build democratic institutions of society and government which will permit them to achieve their highest aspirations.

Now, coming back to the economic area and the important thought that I have hoped to leave with you: it is that each of these misunderstandings has a direct bearing on the substantive problems that must be solved.

Let's take their feeling about price-fixing as an example. One of the most serious problems in this hemisphere at the moment has to do with coffee. Fifteen nations of Latin America and six of Africa produce coffee. We import 90% of our coffee from Latin America, 10% from Africa. Not so many years ago, due to a great freeze in Brazil which damaged the crop, there was shortage of coffee. You will recall that the price of coffee in this country went up to $1.25 per pound and even higher.

Since that time production has outstripped consumption. There are now serious surpluses of coffee in the producing countries and the price has gone down sharply in those countries—to about 40 cents a pound. The Foreign Minister of Colombia told me that every time the price of coffee drops one cent it reduces the income of his country by $8 million, which has a very serious effect in a small country dependent on one crop for the welfare of its people.

Now, when the price of raw coffee goes down, it may lower the final consumer price a little in this country, but I doubt that this actually does us any good. It is a tragedy to the producing country, which is compelled to buy less in manufactured goods from us—for it will no longer have the dollars to do so. Then both of us are disadvantaged.

One difficulty in building understanding in the United States about this kind of problem is that the economic disadvantage to us is so widely diffused that its effect is not strongly felt. Colombia may buy somewhat fewer cars, fewer typewriters and telephones and toothbrushes and all the other things that we manufacture in this amazing industrial system of ours, but as I say, the dis-

advantage is so widespread that we don't feel it. But the concentrated disadvantage with respect to coffee in the producing countries is so great that, believe me, their people do feel it.

The Latin American nations producing coffee today are asking for the development of a marketing agreement which they hope will stabilize coffee prices. The United States has not been willing to agree to one, and I am sure that, believing firmly in the principles of the competitive enterprise system as we do, our minds rebel against such an idea. But this problem has now become so serious to Latin America that we must help in ways that we can. Don't forget that ours is a relationship between nations indispensable to one another—one producing raw commodities, the other producing manufactured goods.

Further, it so happens that on two occasions—with respect to wheat and sugar—when it was in our self-interest to do so, we agreed to international marketing agreements. The question now is: are we going to have a different attitude when the commodity is one in which fifteen of our firmest friends are deeply concerned?

I think, myself, that if they develop a marketing program and want our cooperation to the extent of providing information essential to preventing bootlegging around the quotas, we should cooperate. My fear is not in cooperating to this extent in such a program but that they will put too much faith in it. The best a marketing agreement can do is to stabilize prices for a time. If prices are stabilized at a satisfactory level it will encourage even greater surplus production, and eventually—as we have learned in our own national agricultural program—the surpluses will pile up and up. In this country alone it costs us $1 million a day just to store our agricultural surpluses.

So, if a marketing program for coffee is instituted, certainly we must do everything we can to have the producing nations understand that they cannot put much faith in it except for a temporary period, so that they will devote their attention to finding the real solution: lowering the costs of production, finding new markets, and shifting high-cost coffee acres to other commodities which will enrich and diversify their diet or which they can sell for foreign exchange.

I have used the coffee situation just as an example, to illustrate the point that we must do what we reasonably can to assist the Latin American nations with their economic problems, since we share a common interest in their prosperity and well-being. Again I would emphasize that we must eliminate the serious misunderstandings which impede constructive and mutually beneficial cooperative action.

Their misunderstanding of our economic capacity and their lingering belief that we believe other areas to be more important to our future has a direct bearing, of course, upon their vast and almost insatiable desire and need for credit. In general, Latin America is today about where we were in the early years of our industrial revolution. It is true that in some of the countries they have neglected their agriculture, though fortunately they are making great strides both in research and in the spreading of scientific practices. But no one can travel through Latin America without realizing that she cannot keep up with the march of events unless she industrializes at a much more rapid rate than now.

The population of Latin America is the most rapidly increasing of any area of the world, about 3% a year. Even though their productivity is increasing at an exceptional rate, it is barely keeping up with the increase of population. Thus no increase is made in the standard of living of their people. To solve this problem they need capital for development and they need it in large volume.

Now, briefly, I think three new things are needed if we are to be helpful.

First, each Latin American nation must do a better job than it has done heretofore in developing a complete economic analysis of its potential, and drawing up a development program, with priorities assigned within that program. These priorities are essential—because the private and public credit institutions of this nation cannot satisfy all the demands at any one time; nor could Latin nations absorb, without the most serious economic dislocations, such volumes of credit at one time. They therefore need to determine priorities and feed the credit into de-

velopment in proper order, so that one loan may develop a program which will support and benefit yet another, with a snowballing effect.

Some nations have made excellent preparations of this sort; others are quite deficient. To prepare sound development programs, the Latin American governments need technical help, and they need assistance in locating appropriate sources of credit. Once they have done their analysis and planning, they then face a great array of credit institutions which only the most sophisticated borrower can comprehend: the World Bank can make development loans guaranteed by governments. Associated with it is the International Finance Corporation, which under certain conditions can make loans to private competitive enterprise. The Export-Import Bank may make loans involving dollar expenditures, provided the loans are repaid in dollars. The Development Loan Fund can make loans that can be repaid in local currency.

All these sources put together have been providing only 20% of the credit; 80% comes from private institutions. It is on these private institutions that Latin America largely must depend.

A second thing needed is an intelligent coordination of the lending institutions, so that a nation in Latin America which wants and deserves help can go to a single place for consideration of its total plan in terms of both public and private sources of credit.

Third, we in the United States need to take a positive approach toward their needs and to use credit as an instrument for forwarding our national policy in our desire to help them.

Just a word more about private credit. A good many people in Latin America have some objections to private credit, in the belief that it is almost by definition imperialistic. This view is fomented by Communists wherever and whenever they have the opportunity. The argument is that if an enterprise in a Latin American country is wholly privately financed, that government loses control over it. Of course, this is nonsense. In the development period of the United States, from the beginning of our history down to 1878, we drew enormous sums of private credit from Europe. Public credit then was almost unknown. That private credit contributed mightily to the development of our country. It did not impair our sovereignty one bit. By the way, not until 1918 did we pay off the debt. We have been a creditor country for only forty years.

Latin America is now in the same condition we were in when we were drawing capital from Europe. Private capital is not imperialistic. Further, it exists in abundance and it is superior to public credit in that it carries with it management skills which can be a decisive factor, particularly in the early stages of new development projects.

In 1953, when I began my studies in this area, I was greatly disturbed by unbalanced budgets, inflation, nonconvertibility of currencies and economic dislocations caused by these forces. I was happy to observe this summer that Latin American leaders are now expressing genuine concern about policies that cause instability. They are taking pride in balancing budgets and stabilizing currencies and keeping them convertible. To me, this is a very helpful sign.

But the most hopeful thing I have observed is the development of the common market concept. May I dramatize this by telling you what a very intelligent man in El Salvador said to me?

"What do you think would have happened to the United States," he said, "if your 48 States had been independent nations, each with tariff walls around it, each with its own currency, each maintaining diplomatic missions around the world? You would never have developed large mass-producing higher quality goods at lower costs, selling to masses of people at lower cost than they had ever dreamed they could get. You would be like us."

Just think. El Salvador is not as large as the State of Maryland, where I now live; and I asked myself: what would Maryland be like if it were independent with its own currency and tariff walls?

Fortunately, the countries of Central America have signed a treaty agreeing to the common market concept. This is good. If a steel industry locates in El Salvador and can sell only to El Salvadorians, it has little

chance to succeed; but if it can sell to all of Central America, also perhaps to Panama and maybe ultimately even to the northern tier of South America, it can succeed. A tire factory can locate in Guatemala, a paper and pulp mill in Honduras, and so on —each selling to a larger market and developing genuine efficiency. Further, if they do this, both private and public credit institutions will be more enthusiastic in helping them.

Ladies and gentlemen, a discussion of this kind is a very discouraging sort of experience for both of us because I am sure I have given you nothing more than a superficial glance at the many problems bearing upon Latin American-United States relations.

But I do express a faith to you: I am not only convinced that no other area of the world is more important to us than Latin America, but that by working together intelligently, the nations of this hemisphere can progress mightily, and jointly can maintain peace among the American republics. Thus this hemisphere can set standards for all the world to emulate.